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THE ATTITUDE OF MEDICAL SOCIETIES TO PREPAID GROUP PRACTICE*

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NEW YORK CITY

WHEN people become emotionally disturbed, they often lose the power of logical reasoning. The commonest cause of such emotional disturbances in everyday life is fear of the unknown. These two simple observations explain the unreasonable emotionalism that often moves a large portion of the medical profession, sometimes even a majority, to resist violently and often illogically almost any changes in the organization of medical care and public health.

This was the original reaction of many physicians to the establishment of full-time county health departments, to communicable-disease clinics, to full-time professorships at medical schools and teaching hospitals, to the medical provisions of the Workmen's Compensation Act, to contract physicians in industrial medicine and to a host of other changes now universally accepted by the medical profession as standard medical and public-health practices. These fears of the unknown ultimately faded away in the light of experience.

Physicians as a class are extremely conservative. The attitude of caution is actually cultivated by them as a necessary feature of their daily professional life, and, on the whole, it is a desirable asset. It is therefore important that an effort be made to meet the hostility of some of the critics in the medical profession with calm understanding, with dignity and without rancor.

The consumer-sponsored and community-sponsored insurance plans united in the Cooperative Health Federation of America (CHFA) are dedicated to two basic concepts: that the public requires *comprehensive* medical care at a cost that people can afford to pay and that the ready availability of such comprehensive medical services to ambulatory persons is vitally important for prevention and early detection of disease. In this age of highly specialized professional skills and medical technology, the total medical needs of a population can best be met by a well balanced group of physicians, specialists and technicians trained in the variety of skills and technics that today constitutes modern medicine. The purpose of the member organizations in CHFA is to combine these medical skills and technics in the form of group practice so as to be able to place them freely at the disposal of people of moderate means in return for the income received from their insurance premiums.

If the reasons for the violent opposition by some members of the medical profession to prepaid group practice of medicine are analyzed, a paradox is evident. Group practice of medicine on a fee-for-service basis is tolerated and even admired today by most doctors. The entire profession also strongly advocates voluntary medical insurance. Yet many physicians and some local medical societies violently disapprove of the combination of group practice with prepayment and do everything they can to prevent or destroy it. The explanation for this seeming paradox is not far to seek.

Prepaid group practice is able to offer the public something that individual practice cannot provide on an insurance basis — namely, prepaid medical care of comprehensive scope in the homes of the insured, in doctors' offices and in the medical group's center, as well as in hospitals. The medical care to which the insured are entitled also includes preventive health services and facilities for early detection of disease. It can be so thoroughly comprehensive in its insurance coverage that there is seldom need for the insured to make additional payments to physicians outside the medical group. If satisfied with the full scope and quality of the medical care provided for them by the medical group, the insured are completely out of the general medical market. There is no more money to be made out of this part of the population. Therein lies the true cause of complaint and resistance by the opponents of prepaid group practice.

When a doctor loses a patient to a medical group, he is often resentful toward the group because he knows that it possesses many advantages over him. It can give patients the services of a family doctor and also the benefit of its complete laboratory and x-ray facilities and of all its consulting specialist

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services. Insured families that receive all their medical services from a prepaid medical group can completely budget all their costs for medical care throughout the year. These constitute such significant benefits that physicians who practice in independent isolation under a fee-for-service system of remuneration are under a great competitive disadvantage.

To the extent that they lose some of their former patients to a prepaid medical group, physicians are injured financially. It is therefore understandable why they become emotionally disturbed. A feeling of frustration comes over them because they dare not reveal to the public that their opposition to prepaid group practice is purely economic. To hide their actual motives, they seek some other basis for attack, usually in the code of medical ethics. If they fail to find what they seek in the existing code of ethics, they sometimes proceed to amend the code to suit their purposes. As the members of the CHFA well know, this has actually been done by some county and state medical societies in several parts of the country — most recently in New York. This device has been used in spite of the pronouncements of the Judicial Council of the American Medical Association,[1] the Twenty Principles adopted by the House of Delegates of the AMA for the approval of lay-sponsored medical insurance plans[2] and editorial advice in the *Journal of the American Medical Association*.[3]

Prepaid group practice of medicine has been labeled unethical by some local medical societies because the insured persons who receive their medical care from a medical group do not have "free choice of physician." This reasoning ignores the superior benefits that insured persons may derive from the combined professional staff and physical facilities of the medical group. It also ignores the fact that the subscribers have exercised choice when they elected to obtain their medical care from a prepaid medical group. If they change their minds after they have joined, they are at liberty at any time to discontinue their subscription and choose any doctor outside the plan whom they prefer and can afford to pay. They have free choice like the rest of the population.

In actuality, the members of the medical profession who endeavor to eliminate prepaid group practice and make it unavailable to the public are themselves the real opponents of "free choice." They are endeavoring to destroy the only form of prepaid medical care that can provide comprehensive coverage to insured persons, with all its advantages of economy, preventive services and facilities for early detection of disease. If they had their way, they would deny the public any opportunity to budget all the annual costs of family medical care. They would leave the public no choice but medical-expense indemnity insurance with coverage so limited that doctors might levy extra charges for 90 per cent of all medical conditions treated outside a hospital. By limiting the scope of voluntary medical insurance in this manner, they unwittingly encourage public demand for governmental intervention.

The defenders of the *status quo* also frequently attempt to justify their opposition to prepaid medical group practice by claiming that it is the entering wedge to "socialized medicine." They forget that medical group practice is a characteristically American invention, examples of which have existed in this country for decades. The accusation was again leveled at the Health Insurance Plan of Greater New York a few weeks ago by the retiring president of a county medical society who personally disapproves of prepaid group practice. In replying to this physician, Mr. Gerard Swope, formerly president of the General Electric Company, made the following statement in the *New York Times* of May 30, 1952:

> As one of the founders and at present a director of the Health Insurance Plan of Greater New York (H.I.P.), which was established to encourage prepaid group practice, I should like to lay at rest the specter of "socialized medicine" which he raised by recalling to your readers that H.I.P. is a voluntary non-profit insurance plan incorporated under the insurance laws of New York State. As the subscribers or their employers or both pay the insurance premiums, there is not the least taint of "socialized medicine."
>
> The Health Insurance Plan, which was established by community leaders five and a half years ago as a voluntary non-profit agency to fill an unmet community need, is a demonstration that completely prepaid medical care of truly comprehensive scope can be provided at low cost to insured families under our free-enterprise system.
>
> Its success in meeting the full medical needs of an insured population of more than 300,000 persons will do far more to prevent governmental intervention in the field of medical care, so-called "socialized medicine," than millions of dollars spent in propaganda.

Governmental intervention in the field of medical care will come to pass in the United States and the country will have compulsory medical insurance if the opposition of physicians continues to interfere with the growth of the only form of voluntary medical insurance that can meet the full medical needs of the people. In New York, the obstructive tactics of some local medical societies are now following the identical pattern heretofore employed by local societies to interfere with prepaid group practice in the District of Columbia, the states of Washington, Oregon, California, Oklahoma, and many other parts of the country. In spite of continued harassment, I know of no prepaid group-practice organization against which the local societies have been successful.

In spite of the extraordinary difficulties encountered during its first five years, there are now 31 HIP medical groups in successful operation — 30 located in various sections of the five boroughs of New York City and 1 in the adjacent county of Nassau. Together they comprise almost 1000 general practitioners and specialists. By July 1

they will be providing comprehensive medical care to more than 340,000 persons and before the end of 1952 the insured population will exceed 400,000.

Medical group practice, as exemplified by the organizations in CHFA, is a logical development of the present day and age. As the New York Academy of Medicine has indicated,[4] it is the evolutionary outcome of "medicine in the changing order." The comprehensive benefits of such medical group practice can be made available to families of moderate income only if the cost is shared by the enrolled persons on an insurance basis. Since medical societies cannot or will not provide the public with the opportunity to purchase comprehensive medical care in the form of prepaid group medicine, it must be established at local levels by insurance plans sponsored either by consumer organizations or by public-spirited community leaders. In the spread of this significant undertaking, the CHFA has assumed a most important public responsibility.

For many years my friend the late Fiorello H. LaGuardia, while mayor of the City of New York, began and ended each of his Sunday noon radio broadcasts to the public with the words "Patience and Fortitude." The good Fiorello, one of the founders of HIP, was certainly well endowed with fortitude — although he was not specially noted for his patience. Physicians engaged in prepaid group practice should adopt his slogan as their own and promise one another to carry on with "patience and fortitude."

7 East 12th Street

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ATYPICAL MANIFESTATIONS OF PERIPHERAL ARTERIOSCLEROSIS*

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THIS paper considers certain of the more atypical manifestations of peripheral arteriosclerosis and their management. These include murmur production in the peripheral arteries, syndromes of ischemia in circumscribed arterial territories and the peculiar effects of venous thrombosis in the ischemic limb.

Murmur Production in the Peripheral Arteries

That a murmur may be heard over an arteriosclerotic vessel was mentioned by Sahli[1] and has recently been emphasized for the aorta by Hiestand and Morris[2] and by Popkin.[3] Recent work on murmur production has established the value of auscultation in the diagnosis of arteriosclerosis, localizing the site of greatest involvement and, in some cases, proving the existence of a patent lumen.[4] Auscultation has been supplemented by phonangiography or visual registration of the sound and by x-ray angiography. In my experience, partial narrowing is much more effective than aneurysm formation in producing a murmur. This is probably due in part to the parietal-thrombosis characteristic of aneurysm, which makes the diameter change less abrupt and also acts as a poor conductor for the vibrations.

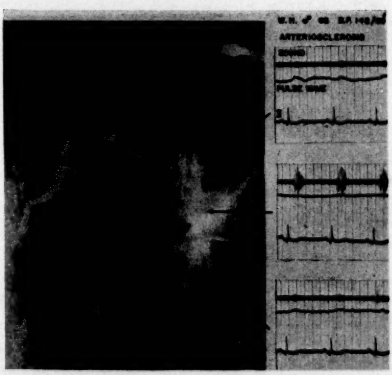

Figure 1. *Sound and X-Ray Arteriograms. The systolic murmur is loudest in the middle set of tracings taken from the lower segment of the narrowed external iliac artery. The film shows obstruction of the parietal branches of the hypogastric arteries responsible for claudication of the hip in this patient (reproduced from Edwards and Levine,[4] with the permission of the publishers).*

The murmur of partial stenosis, systolic in time and rough sounding, and occasionally accompanied

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by a thrill, is present in about half the patients with arteriosclerosis. The murmur is oftenest heard over the femoral or iliac arteries, sometimes over the abdominal aorta (Fig. 1 and 2). X-ray angiography always demonstrates some lumen when the murmur is heard, often when no pulse is apparent. In general, the murmur is loudest when the obstruction is severe, although short of complete. It is also intensified and prolonged by a high pulse pressure. In some patients the murmur disappears as arterial obstruction becomes more complete and ischemia more pronounced.

The murmur is of special diagnostic value when other signs of peripheral ischemia are minimal.

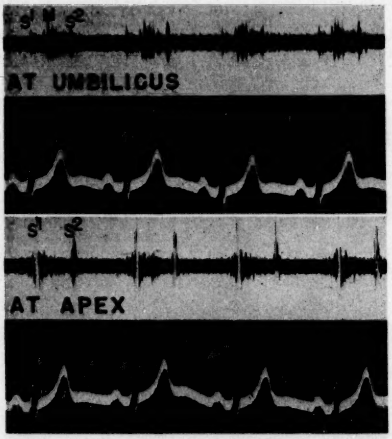

FIGURE 2. *Systolic Murmur* (M) *over the Bifurcation of the Aorta in a Fifty-Four-Year-Old Man with Aortic-Hypogastric Syndrome — the Patient Shown in Figure 6A.*

S^1 and S^2 are the transmitted heart sounds as shown by the tracing taken at the cardiac apex. The blood pressure was 134 systolic, 78 diastolic.

Figure 3 shows the murmurs of aneurysm and of arteriovenous fistula. The murmur of aneurysm is also systolic, but evident enlargement of the artery easily leads to the correct diagnosis. The murmur of arteriovenous fistula is continuous, although with systolic accentuation. I have not observed a murmur in arteries affected by Buerger's disease. An abrupt protosystolic-impact sound is encountered proximal to the complete obstruction of an embolus or thrombus only when the pulse pressure is extremely high.

SYNDROMES OF ISCHEMIA IN CIRCUMSCRIBED ARTERIAL TERRITORIES

Although the arterial branches of the lower extremity are not end arteries, some tissues depend on one or a limited number or portions of such vessels. For this reason ischemia may develop in some areas even when the main trunk remains

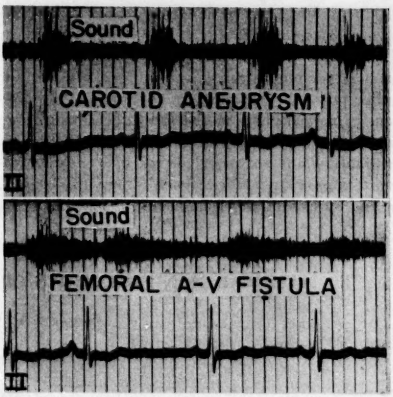

FIGURE 3. *Sound Tracings over an Aneurysm of the Internal Carotid Artery in the Neck, and over a Femoral Arteriovenous Fistula, Both in the Same Patient, a Seventy-Seven-Year-Old Man.*

The murmur of the aneurysm resembles that of arteriosclerotic narrowing, but the murmur of the fistula extends throughout the pulse cycle, although accentuated during systole. The blood pressure was 220 systolic, 80 diastolic.

open. Some clinical examples of arterial obstruction in localized portions of the skin, musculature and nerves deserve mention.

Localized skin necrosis may follow some extrinsic insult, or may occur as a seemingly spontaneous infarction.[5] When the spontaneous lesions are small, they resemble the "hypertensive ischemic" ulcers described by Hines and Farber.[6] Thrombosis of fine vessels seems responsible for some of these lesions, and unrecognized infection for others. Infarctions under 1 or 2 cm. in diameter may heal spontaneously, but larger ones are apt to be progressive and to lead to amputation. When the lesion is located on the leg, good results have been obtained by wide excision of the infarction and the areola of discolored skin, with split-thickness skin graft and lumbar sympathectomy, preferably all done at one stage (Fig. 4 and 5).

The arterial supply of an individual muscle has no significant connection with the vessels of neighboring structures.[7] For this reason, muscles sup-

plied by a single artery may be subject to severe ischemia, whereas the remainder of the limb is affected only slightly or not at all. Examples of acute ischemia include contracture and atrophy

FIGURE 4. *Spontaneous Cutaneous Infarction in a Diabetic Woman with Arteriosclerosis.*
A *shows the lesion ten days after onset, with central necrosis and areola of infection. In* B *the arrow points to almost complete obstruction by atheroma of a genicular artery supplying the area.* C *shows successful split-skin grafting applied in mosaic fashion, after excision, lumbar sympathectomy and division of a varicosed saphenous vein, done at one sitting.*

of individual muscles after thrombosis of small arteries, as well as necrosis of the entire gastrocnemius muscle when gangrene of only the foot is present. Occasionally, also, when a mid-thigh

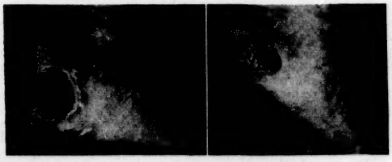

FIGURE 5. *Spontaneous Cutaneous Infarction* (A) *in a Diabetic Man with Kimmelstiel–Wilson's Disease.*
A faint dorsalis-pedis pulse was present. Excision and split-skin grafting were followed by slough of the graft. This was removed, and successful pinch grafting accomplished (B).

amputation is being performed, the sartorius and vastus medialis muscles will be found to be necrotic up to their origins, and the other structures may be necrotic to just above the knee.

Chronic ischemia may involve muscle groups supplied by individual branches of the main arterial stem. Obstruction of the parietal branches of the lower aorta and of the hypogastric artery gives rise to claudication and pain in the lower back and hip, with atrophy of the muscles of these regions (Fig. 6*A*). This has been ascribed to occlusion of the lower aorta itself, but this vessel proper and the external iliac arteries may be patent (Fig. 1). Indeed, since only the parietal branches need be occluded, the disease may develop unilaterally (Fig. 6*B*). The term aortic-hypogastric syndrome is suggested instead of the usual term aortic. Occlusion of the deep femoral artery gives rise to claudi-

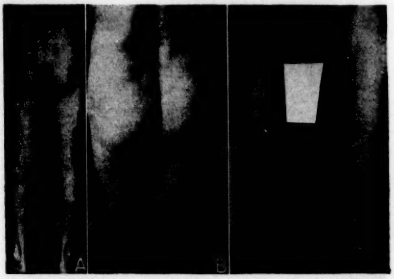

FIGURE 6. *Muscle Atrophy Due to Arteriosclerotic Occlusion of Specific Arteries.*
A *shows occlusion of lower aorta and hypogastric arteries (sound tracing of same patient in Figure 2),* B *shows occlusion of the right common iliac artery (arrow points to atrophy of the buttock), and* C *shows occlusion of the left deep femoral artery (arrows point to atrophy of adductor and quadriceps muscles): the main arterial trunk remained patent, with good dorsalis-pedis pulsations.*

cation and pain in the medial part of the thigh, with atrophy of the adductor muscles. The quadriceps muscle may share in these symptoms (Fig. 6*C*), depending on whether the lateral femoral circumflex artery, which is a major source of supply to the quadriceps muscle, arises from the deep femoral, or, as in 18 per cent of cases, from the common femoral artery.

In such cases, as well as in patients without clear-cut evidence of obstruction of the branches mentioned, patients may complain of claudication, although the pedal pulses remain palpable. The explanation apparently lies in obstruction of muscle arteries while the major trunk remains patent. The diagnosis is based on the typical nature of the claudication, and the presence of one or more of the following signs: coldness or blanching of the foot; asymmetry of the pulses (which are occasionally normal, however); great disproportion of the oscillometric measurement of pulse amplitude

and pressure in the two limbs; and a systolic murmur in the major arteries. Of 24 patients studied, further evolution of the arteriosclerosis led to later obstruction of the aorta, common femoral or popliteal arteries in 5.

I have not encountered complete interference with nerve function as a result of localized ischemia caused by arteriosclerosis. Lesser degrees of neuritis, however, are fairly frequent in the sciatic, peroneal or tibial nerves, and are characterized by hypesthesia, paresthesias and slight degrees of muscle weakness in the region of these nerves. Fetterman and Spitler[8] and Roberts[9] refer to such cases in their reports on ischemic neuritis. The osseous and cutaneous lesions of diabetic neuropathy healed after sympathectomy in 2 cases reported by Parsons and Norton,[10] and in 1 of my own cases, but this does not prove the vascular nature of this form of neuritis, since anesthesia and muscle weakness remained.

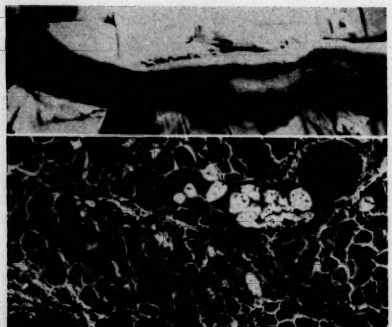

FIGURE 7. *Gangrene Precipitated by Venous Occlusion in the Presence of Old Atherosclerosis. (Case 2).*

The photograph shows the dark (blue) appearance of the leg. The section of the infarcted gastrocnemius muscle demonstrates the necrosis, extensive venous thrombosis and hemorrhage.

Venous Thrombosis in the Ischemic Limb

On theoretical grounds, the arteriosclerotic limb, with its slowing of the blood stream and interference with nutrition, provides ideal circumstances for the development of venous thrombosis. It is therefore not surprising to find some venous thrombosis, although often of minor degree, in almost every limb that is amputated.[11] Arteriosclerotic ischemia may be looked upon as sufficient cause for such a process, and cases showing no other cause for the thrombosis need not be considered idiopathic.

With the lack of vitality characteristic of ischemic tissue, organization of these thrombi is delayed, and pulmonary embolism is particularly apt to occur. Frequently, arteriosclerotic patients may thus be seen with pulmonary embolism as the presenting problem. Pulmonary embolism is also a frequent postoperative complication of sympathectomy performed for the correction of ischemia.

A second and less common effect of the venous thrombosis in these cases is the precipitation of gangrene, which has been noted in 6 patients. The gangrene seems so clearly related to the obstruction to the outflow of the already enfeebled stream that, so far as possible, anticoagulants seem the treatment of choice. Nevertheless, the occurrence of pulmonary emboli may necessitate venous ligation. The following cases are illustrative.

Case Reports

Case 1. A 64-year-old woman suffering from arteriosclerotic heart disease failed to regain adequate strength after a cholecystectomy for acute cholecystitis. On the 14th postoperative day, duskiness of the right foot developed, quickly progressing to frank gangrene and requiring supracondylar amputation. Soon the left foot became gangrenous and was also amputated.

Examination of both specimens showed extensive atherosclerosis but persistent small lumens in the major arteries and no fresh occlusion. The veins were extensively thrombosed in both limbs, with typical hemorrhagic infarction of the muscles.

The patient died 10 days after the second amputation. Autopsy revealed the cause of death to be acute myocardial infarction without fresh coronary thrombosis.

Case 2. A 59-year-old man had been treated elsewhere for pulmonary embolism of unknown origin. With a second attack the left calf was observed to be tender, and a division of the left superficial femoral and saphenous veins was performed. Sclerosis of the left femoral artery and lack of a pulse below this level were noted.

He came under observation after a third embolism. A bilateral common-femoral-vein ligation was done, thrombus being found in the left vein and aspirated. When the anticoagulant was changed from heparin to Dicumarol on the 3d postoperative night, the left limb suddenly became violently painful, swollen, blue and lifeless. By morning, gangrene of the foot and lower two thirds of the leg was apparent (Fig. 7). Amputation revealed thrombosis of all the veins below the level of demarcation, with hemorrhagic infarction of the muscles (Fig. 7). The popliteal, tibial and peroneal arteries all showed extensive atherosclerosis and extreme narrowing of the lumens.

Six weeks later this patient had another pulmonary embolism. Ligation of the inferior vena cava was performed. One week after this procedure, when heparin was replaced by Dicumarol, thrombosis of the pelvic veins developed, with distention of the cavernous bodies of the penis and necrosis of the tip of the glans. With continued heparin treatment, the patient recovered without further incident.

Conclusions

Narrowing produces audible murmurs in the peripheral arteries in half the patients with arteriosclerosis.

Areas of skin and individual muscles and nerves are often dependent upon a single or a limited number of arterial branches, and localized ischemia may

therefore develop in these structures out of proportion to the vascularity of the limb as a whole.

Venous thrombosis often occurs in the arteriosclerotic limb. It is particularly apt to give rise to pulmonary embolism or to precipitate gangrene.

330 Dartmouth Street

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AGITATED DEPRESSION ASSOCIATED WITH ARTERIOVENOUS ANEURYSM OF LEFT FRONTAL LOBE

Recovery After Unilateral Frontal Lobectomy

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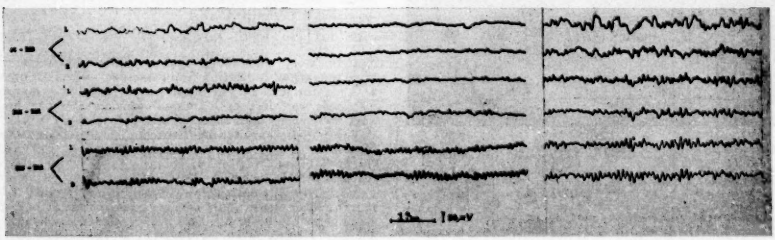
IN THE case reported below, a patient with agitated depression showed remarkable improvement after unilateral left prefrontal lobectomy for massive arteriovenous aneurysm. Not only was the combination of psychosis and massive aneurysm malformation unusual, but, to our knowledge, there are no other reports of recovery from depression after left prefrontal amputation. The case tends to confirm our previous findings that unilateral lobotomy may have dramatic results in some psychotic patients, although unilateral lobotomy is generally less effective than bilateral lobotomy.[1-3]



A B C

FIGURE 1. *Electroencephalographic Tracings.*
A = *Tracing made before operation.* B = *Tracing made two months after operation.* C = *Tracing made seven months after operation.*

Case Report

C. S., a 29-year-old single man, was admitted to Boston Psychopathic Hospital on May 29, 1951, after several suicidal attempts, with symptoms of depression, guilt, psychomotor retardation, occasional agitation and continuing suicidal trends. He had become increasingly depressed since February, after his mother's mental illness. In the middle of March, he showed slowing in speech and motor activity, with loss of appetite and insomnia, and began to complain of "heavy headedness" and mild headaches. Owing to the aggravation of insomnia and headaches, he was admitted to a general hospital, where, after 2 days, he attempted suicide by cutting his throat and wrists. He stated that he felt a strong urge to kill his father and a physician who was taking care of his sick mother. This urge for destruction and the subsequent guilty feelings drove him to attempt suicide. He was transferred to a private sanatorium and subsequently to a state hospital, where no shock treatments were administered because of a history of hemiplegia in 1941. He was referred to Boston Psychopathic Hospital for further study and for decision regarding the advisability of electroshock treatment.

The patient's physical and mental development was average until the age of 19 (1941). In August, 1940, he sustained a head injury after a fall in a boat; he was dazed for a moment, but not unconscious. In January, 1941, right hemiplegia suddenly occurred, and the patient was admitted to the Massachusetts General Hospital. Neurologic findings included right hemiplegia with tongue deviation to the right, motor aphasia, positive Babinski reflex, and ankle clonus. X-ray examination of the skull, electroencephalographic study and spinal-fluid examination were negative. The patient recovered from the hemiplegia in 1 month and from the motor

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aphasia in 8 weeks. He was engaged in clerical work for 3 years and later worked steadily as a printer. He became retiring, bashful, thrifty and passive. He never took a girl out and spent his leisure mostly at home reading magazines.

The patient's mother had 2 episodes of psychosis. The first was in 1941, after the patient's recovery from hemiplegia. The second began in February of 1951, and she was admitted to the Boston Psychopathic Hospital with the diagnosis of involutional psychosis and melancholia. The patient's maternal uncle had committed suicide at the age of 27.

The patient exhibited guilt about his attempted suicide. He felt inferior and unworthy, stating that he was not good enough for the hospital and the good food. At times he became agitated and restless, wanting to escape or kill himself, so that restraint was needed. At other times, he showed lack of motor activity and retardation of speech. His suicidal ideas, with agitation and psychomotor retardation, became aggravated to the extent that he was restrained and fed by tube for several days.

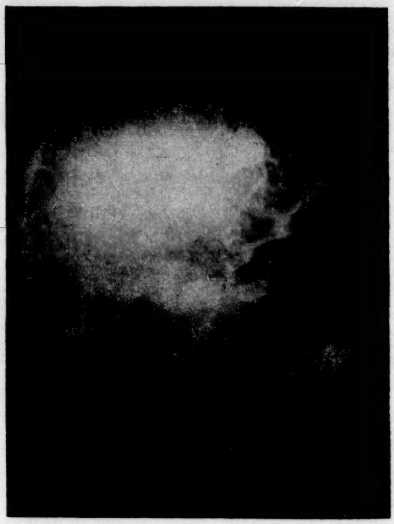

FIGURE 2. *Arteriogram, Showing Arteriovenous Aneurysm.*

The only positive neurologic sign was a mild paralysis of the right lower facial nerve. An electroencephalogram showed scattered mild slow waves, mostly from the left precentral cortex (Fig. 1*A*). An arteriogram demonstrated an arteriovenous aneurysm, 3 cm. in diameter, deep in the middle portion of the left frontal lobe (Fig. 2). It was concluded that shock treatment would be too risky to employ but that removal of the aneurysm should be attempted. Operation was performed on June 19.

After the scalp, bone flap and dura had been turned back, a cortical incision was made 6 cm. behind the tip of the frontal lobe. Then the left anterior cerebral artery, which apparently was the main feeding vessel to the aneurysm, was clipped. Finally, the portion of the left frontal lobe that contained the aneurysm was excised. Examination of the slides of the lesion revealed the classic picture of arteriovenous aneurysm of the brain.

Upon recuperation from the operation, the patient began to show marked changes in his mental status. He became cooperative and more talkative; the preoperative psychotic symptoms, such as depression, feelings of guilt and suicidal impulses, disappeared. For about 1 month, he had delusional ideas that he had 5 grandchildren, that there was a devil on the ward and that he was homosexual. He actively participated in the recreational events and, for the first time, danced with student nurses upon invitation. As his social adaptation improved, the delusional ideas diminished, almost disappearing in about 2 months. He seemed more cheerful and alert and had gained about 30 pounds. The only abnormal sign was a motor aphasia; he had considerable difficulty in choice of words, and very slight difficulty in understanding words. These impairments improved progressively during hospitalization.

After discharge, on August 22, the patient was followed for 10 months. He made a good adjustment, first to life at the convalescent home (Gould Farm) and later to life with his family. He took a speech course to improve his speech deficiency and a course in mineralogy for his own interest. Remarkable recovery of speech capacity was noted, both subjectively and objectively. He wanted to go back to work and to be of some help to sick people. He gained 20 more pounds after discharge.

Three Bellevue-Wechsler intelligence tests were done on March 10 and July 30, 1951, and on January 9, 1952 — one at the onset of depression, while the patient was outside the hospital, and two after lobectomy (1 month and 7 months postoperatively). Table 1 shows impairment in digit memory and block design before and immediately after operation, indicating brain damage. The improvement at 7 months may be attributed to resolution of symptoms of psychosis and loss of emotional tension. Similar findings have frequently been reported after lobotomy.[4]

TABLE 1. *Results of Bellevue–Wechsler Test.*

COMPONENT OF TEST	RESULT		
	3 MO. BEFORE LOBECTOMY	1 MO. AFTER LOBECTOMY	7 MO. AFTER LOBECTOMY
Comprehension	13	15	16
Information	15	15	17
Digit memory	7	7	10
Arithmetic	13	13	12
Similarities	14	15	14
Picture arrangement	14	15	16
Picture completion	12	12	15
Block designs	10	10	14

The patient experienced two convulsive seizures, one on November 8, and one on December 20, 1951. He has been taking 0.09 gm. (1½ gr.) of Dilantin three times a day since the first attack.

Electroencephalographic examination on August 8 (1½ months after operation) was negative, the previous minor asymmetry of the hemisphere having disappeared (Fig. 1*B*). Another electroencephalogram, taken on January 9, 1952 (after the patient's two seizures), showed a prominent slow-wave focus centering around the left precentral area, but with typical seizure pattern (Fig. 1*C*).

DISCUSSION

This patient presented a classic picture of arteriovenous malformation. The hemiplegia in 1941 was apparently caused by rupture of the aneurysm, which, however, was not discovered at that time. The head injury of 1940 may have been from the same cause, but there is insufficient evidence on that point. The unusual feature was the association of aneurysm with the depressive agitation that precipitated hospitalization.

The question of the relation between the mental depression and the process in the left frontal lobe

is an interesting one. The onset of depression coincided with the onset of subtle clinical manifestations of the aneurysm, such as headaches. The dramatic recovery from depression after removal of tumor suggests that the mental symptoms were related to the tumor in the frontal lobe. However, neither present knowledge concerning the functions of the frontal lobe nor clinical experience regarding aneurysm in the frontal lobe (Dandy,[5] Olivecrona and Riives,[6] Robertson[7] and Rylander[8]) permits one to assume any causal relation between the tumor and the depression.

Whatever the etiologic relation, there is no question that the effect of removal of aneurysm with the left prefrontal lobe was dramatic. The patient not only recovered from the depression but also regained his mental and physical capacities, showing strong initiative and good interpersonal relations.

Opinions concerning the effect of unilateral lobectomy on the psychotic personality differ. Jefferson,[9] Stooky, Scarff and Tietelbaum[10] and Penfield and Evans[11] reported cases of unilateral lobectomy with no subsequent personality changes. On the other hand, Rylander[8] presented cases showing personality defect after unilateral lobectomy. However, since most of the cases concerned neoplasm in frontal lobes, one had to consider the possibility that the other side was affected by the tumor because of pressure and consequent circulatory disturbance, together with some damage caused by the operative procedure. The prevailing opinion has been that both frontal lobes must be damaged to produce personality changes. This motivated Peyton, Noran and Miller[12] to initiate bilateral lobectomy for mental disorders (chiefly schizophrenia) and several authors to try bilateral lobotomies with good results (Freeman and Watts,[13] and Mixter, Tillston and Wies[14]).

The search for modified or limited psychosurgical operations, motivated by the defects in mental functioning in many patients subjected to the full bilateral lobotomy, led some workers to try unilateral frontal lobotomy in chronic mental illness. Perhaps the first of these was Lyerly,[15] who stated that a good unilateral lobotomy might be as effective as a partial bilateral lobotomy. Scarff's[16, 17] report of successful relief of pain from cancer also focused attention upon the possibilities of the unilateral operation. Bockoven and Greenblatt[1] found satisfactory results after unilateral lobotomy in 4 cases of chronic mental disease. This led to a broader investigation of unilateral lobotomy, reported in 1952.[3] Marked improvement was observed in 21 per cent and moderate improvement in 7 per cent of patients. However, the operation seemed definitely inferior to bilateral lobotomy, which has been preferred in cases of chronic mental disease. Recently, Margolis and his co-workers[18] reported the successful use of unilateral lobotomy in less severe neuroses and depressions than the cases studied by the Boston group.

The specific indications for unilateral lobotomy for either mentally ill patients or those with intractable pain have yet to be worked out; however, it has been clearly established that unilateral prefrontal leukotomy or lobectomy may alter personality and behavior profoundly. This is strongly supported by the case reported above.

Summary

A case of massive arteriovenous aneurysm, with the unusual feature of association with agitated depression, is reported.

Remarkable recovery from depression followed prefrontal lobectomy with removal of the aneurysm.

The effectiveness of unilateral frontal-lobe surgery for the treatment of psychoses is discussed.

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LEPROMATOUS LEPROSY

Report of a Case Observed in Massachusetts

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CASES of leprosy (Hansen's disease) are rarely seen in New England. For this reason we believe it worth while to report a case of lepromatous leprosy. The physician unfamiliar with the symptoms of the disease is unlikely to make the proper diagnosis since he is not aware of the possibility of encountering this rare malady.

Clinical classification of the different types of leprosy is difficult. The International Leprosy Congress of Cairo,[1] in 1938, accepted the classification of lepromatous (cutaneous), neural and mixed types of leprosy. The International Leprosy Congress of Havana, Cuba,[2] in 1948, adopted the division of cases into two "polar" types, lepromatous (malignant, or gravis), with the symbol L, and tuberculoid (benign, or mitis), with the symbol T — and an additional group, indeterminate (undifferentiated), with the symbol I. This later classification is based on clinical, bacteriologic, immunologic and histopathological findings.

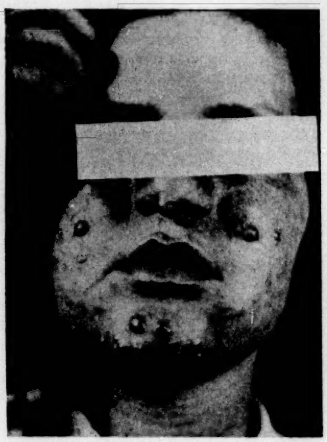

FIGURE 1. *Nodules of Lepromatous Leprosy on the Face and Hands.*

The nodular shiny appearance is demonstrated.

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CASE REPORT

The patient, a 13-year-old girl of Greek extraction, was born on June 1, 1939, in the southern part of Greece. Her father left Greece for the United States shortly after her birth. During 1939 and 1940, 3 maternal relatives affected with leprosy lived in the same house with her family, which consisted of her mother and 4 other children. Her mother died in 1945. She did not have leprosy. The patient, 3 brothers and 1 sister arrived in the United States in 1947. Although her brothers and sister are free of symptoms of leprosy up to the present time, the patient developed a few nodular lesions of the chin and ears some time in 1950. The lesions gradually became more prominent, and new lesions developed on the upper and lower extremities.

In May, 1952, the face, ears and upper and lower extremities were covered with well defined, round, red-brown nodules of the consistence of rubber and varying in diameter from 0.5 to 1 cm. The surface of the lesions was smooth and shiny. Some of the nodules extended more deeply into the subcutaneous tissue (Fig. 1). There were soft as well as firm cutaneous infiltrations on the upper and lower extremities. The overlying skin of the arm infiltrations had a bluish hue, whereas the skin surface of the infiltrations on the lower half of the legs was deep red as well as red blue. The forehead, upper cheeks, neck, trunk, upper third of the anterior aspect of the thighs and buttocks were free of lepromatous lesions. The skin of these areas was normal. There were no lesions on the flexor aspect of the hands except on the proximal area of the palms. There was hard edema of the dorsa of the feet. The mucous membranes of the nose and oral cavity showed no changes. There was no eye involvement. There was no loss of scalp hair or of supraciliary or ciliary hairs. The inguinal lymph nodes were slightly enlarged; no other enlarged lymph nodes were found. No enlarged peripheral nerves could be palpated. There were no signs of sensory-nerve involvement. The blood Hinton reaction was negative.

Numerous characteristic acid-fast bacilli were found microscopically in scrapings from the nasal mucous membrane and in smears from the tissue juice of nodules cut from the skin (Ziehl–Neelsen stain[3]). Histologic examination of several nodes from the face and arms also revealed numerous leprosy bacilli.

Hematoxylin and eosin stain of a nodule showed a superficial granuloma stretching the overlying epidermis and composed of numerous large macrophages with finely vacuolated cytoplasm, so-called "foam cells." Numerous plasma cells were present, as well as small foci of necrosis with polymorphonuclear and eosinophilic leukocytes. The appearance simulated eosinophilic granuloma of the skin in places. With Campbell's stain, large numbers of acid-fast bacilli were found in the foam cells, frequently packed together in bundles like cigars. The bacilli were slightly shorter and thicker and much more numerous than *Mycobacteria tuberculosis* as usually observed. McManus glycogen (periodic-acid Schiff) stain was negative.

DISCUSSION

There are no definite data known about the incubation period of leprosy. In numerous publications the time varies from several weeks to thirty-two years. According to Rogers and Muir[4] the average incubation period is two years and eight months. These authors also tried to find out if there was a relation between incubation time and the length and intimacy of contact with contagious lepers. They divided 84 cases examined into four groups:

cases of inoculations in which the time was exactly known; cases in which the infection was transmitted when the patient shared the bed of a leper; cases in which an infection resulted when patients lived in the same rooms with lepers; and cases in which the patients had less intimate contact with lepers — that is, children infected by playmates, orderlies or nurses in leprosaria. The average duration of incubation was six months in the first group, one year and eight months in the second, two years and ten months in the third and four years and eleven months in the fourth. The differences in the times of incubation were not due to the nature of the infection but rather to the frequency and favorability of the circumstances with which leprosy bacilli were transmitted from diseased to healthy persons by more or less intimate contact.

When a physician suspects the diagnosis of leprosy in a patient with skin lesions suggestive of lepromatous leprosy, he should make an examination for leprosy bacilli while awaiting the results of histologic examination, which is done in a pathological laboratory and usually takes several days. Sometimes, the bacilli are found in scrapings from nasal mucosa and in smears from skin lesions. In the experience of one of us (A. H.) the "tissue-juice method" gives the quickest and best results in demonstrating leprosy bacilli. Under local anesthesia a nodule is cut off at its base, placed with its base on the surface of a microscopical slide and compressed from both sides with a forceps. The resulting tissue juice is smeared on the surface of several microscopical slides. The smears, which should be thin, are allowed to dry in air, and then fixed over a flame. Staining by the Ziehl–Neelsen method[3] (washing in alcohol should be omitted to avoid too much decolorization) will then reveal numerous acid-fast leprosy bacilli, which can be seen in characteristic cigar-bundles.

In lesions of tuberculoid leprosy, which usually show few acid-fast bacilli, the carbon dioxide method of Unna[5] is recommended. Solidified carbon dioxide is pressed on the site of a suspicious skin lesion for about one minute. The resulting blister is opened, the blister fluid smeared on the surface of a microscopical slide and the smear examined with the Ziehl–Neelsen method.[3]

Summary

A case of lepromatous leprosy in a thirteen-year-old girl of Greek extraction is described.

Microscopical examination of scrapings from the nasal mucosa and of smears from excised skin nodules and histologic examination of nodules established the diagnosis. Leprosy bacilli can be demonstrated microscopically in lesions of lepromatous leprosy with the tissue-juice method and subsequent staining by the Ziehl–Neelsen method.

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MEDICAL PROGRESS

THE CLINICAL SIGNIFICANCE OF AMINOACIDURIA*

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THE observation of an excess of amino acids in urine has received little attention from the clinician. In recent years clinical investigators have noted the finding in various conditions, usually obscure in character, and have attempted to clarify its meaning. In a few diseases the presence of aminoaciduria is leading to new concepts of the nature of the condition studied. Since it appears that aminoaciduria may have importance in the basic understanding of some pathologic processes, a review of current knowledge of the subject is undertaken.

The amino acid nitrogen concentration of the plasma, which remains quite constant at 3 to 6 mg. per 100 cc., represents the amino acids absorbed from the intestine and supplemented by similar fractions derived from the constant interchange of dietary and tissue protein. As indicated in a review by Metcoff and Stare,[1] transient physiologic increases follow ingestion of a protein meal or parenteral administration of amino acid. The liver is the main site of deamination of amino acids. This function is of vital importance and remains unaltered until an estimated 90 per cent of the functional capacity of the liver is impaired. Therefore, usually only in the terminal stages of hepatic insufficiency does this function of deamination become grossly abnormal. Urinary excretion of amino acids, in general, parallels the plasma levels, with notable and interesting exceptions. Usually with a marked rise in blood plasma

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concentration of amino acid nitrogen there is an increased excretion of amino acids. That this does not always occur is demonstrated below in specific circumstances.

The amino acids are usually obtained from dietary sources by peptic, tryptic and enteric digestion of protein. After absorption, some amino acids serve as precursors or constituents of vitamins, co-enzymes, hormones and various detoxication products. Some are converted into tissue proteins, whereas others may be utilized for energy or contribute to the nonprotein nitrogen fraction. An outline of the metabolic implications of the essential amino acids is given by Metcoff and Stare.[1] There is also evidence that amino acids are important in carbohydrate metabolism since they are necessary for the formation of the appropriate enzyme systems in the intermediate phases of carbohydrate metabolism.

In the past, the concentrations of amino acids in biologic fluids have been little studied, as indicated by Peters and Van Slyke,[2] because the analytical methods for amino acid determination in biologic mediums are neither precise nor specific. Furthermore, the concentration of specific amino acids in the fluid studied is usually small and a profound disturbance of the intermediate metabolism of proteins may have a relatively trivial effect on the pattern or concentration of the amino acids in the fluid. Recently, increased interest in the study of amino acid metabolism, as it affects the urine and other biologic fluids, has been aroused by the application of partition chromatography in clinical medicine by Dent.[3, 4] By this method, qualitative study of amino acids in urine became comparatively simple when contrasted to the usual microbiologic procedures. In partition chromatography separation of the different amino acids takes place owing to the varying relative solubilities of the amino acids between water held in the cellulose fibers of filter paper and a solvent, not miscible with water, which is allowed to flow slowly along the filter paper past a point that contains the amino acid mixture. The R_F value, the relative rate of movement of the amino acid to the total movement of the solvent, is constant and characteristic for each amino acid, whose location can be developed with suitable reagents (usually ninhydrin), manifesting itself as a colored spot. As Dent[4] has pointed out, there has really been no clinically practicable method of studying aminoaciduria prior to the application of chromatography to the problem — a technic that should introduce new concepts of amino acid metabolism.

TABLE 1. *Urinary Excretion of Amino Acids in Normal Patients.*

FREE AMINO ACID	EXCRETION REPORTED BY ECKHARDT ET AL.[5]	EXCRETION REPORTED BY HIER[6]
	mg./24 hours	*mg./24 hours*
Isoleucine	13.8	5.9
Leucine	7.2	9.6
Lysine	46.8	33.6
Methionine	4.4	7.8
Phenylalanine	14.0	16.4
Threonine	20.9	24.4
Tryptophane	12.7	24.6
Valine	7.4	4.5
Arginine	9.5	21.3
Histidine	163.0	188.3
Aspartic acid	—	1.3
Cystine	—	87.7
Glutamic acid	—	35.8

There are definite limitations to chromatographic study of amino acid excretion. An increased excretion of amino acids cannot be ascertained by chromatography alone unless one compares the size and intensity of spots from a given aliquot of known nitrogen and creatinine content with the chromatogram of a normal urine with the same creatinine concentration. Quantitative estimation of the aminoaciduria can only be accomplished chemically by an estimation of the total twenty-four-hour urinary alpha-amino-nitrogen by the standard Van Slyke or formol-titration procedure.[2] Because of variations in amino acid content of separate specimens, aliquots for assay should be withdrawn from a twenty-four-hour total pooled specimen. The patient who is being studied should be placed on a low-protein diet (30 to 40 gm. daily) for three days prior to collection of the urine to eliminate dietary factors. Under these circumstances the chromatograms will render significant information and lead to the necessary but more arduous chemical studies, as required, in specific cases.

NORMAL EXCRETION OF AMINO ACIDS

Urine normally contains only traces of free amino acids amounting to 1 or 2 per cent of the total nitrogen.[2] By formol titration, the amino nitrogen concentration of normal urines varied from 10 to 30 mg. per 100 cc.[3] Eckhardt and his associates[5] reported an average excretion in 8 normal subjects of 158 mg. (range from 120 to 199 mg.) free alpha-amino-nitrogen per twenty-four-hour urine excretion. There have been several studies, using various analytical technics, of the excretion of the individual amino acids in urine. Table 1 shows the findings of two recent investigations,[5, 6] including the excretion of the ten essential amino acids for man. These essential amino acids are listed first. The differences noted are probably explained by differences in urine preservation and assay technics. Increasing the protein ingested increased only moderately the excretion of amino acids, whereas diets low in or free of protein do not significantly decrease the amino acid excretion.[5, 7, 8] This indicates the relative stability of amino acid excretion in the normal human being. In the partition chromatogram of normal urine weak bands of glycine and alanine and occasionally another faint unidentified band are found.

It is apparent from experimental studies that most of the amino acid in the glomerular filtrate is

reabsorbed in the tubules. As a general rule, renal clearances of specific amino acids rise progressively as the concentration in the plasma increases. However, Wright[9] showed in dogs that certain amino acids may compete with each other for reabsorption by the renal tubules. Such competition studies indicate the existence of more than one functional mechanism in the reabsorptive process of amino acids. Beyer and his associates[10] showed, by experiments in which one of two pairs of amino acids presented to the tubules for reabsorption approached the functional capacity of the cells to reabsorb one of the pair, that in certain instances competition did exist and in others there was no competition. For example, by such loading studies it was found that lysine and histidine interfered with reabsorption of arginine, whereas leucine and isoleucine did not interfere with arginine or with each other. Under the conditions of this experiment, at least two tubular mechanisms for the reabsorption of amino acids were demonstrated.

Earlier, Pitts[11] had shown that all the amino acids were not absorbed with equal efficiency, and that certain amino acids closely related structurally may be reabsorbed at widely divergent rates. It was believed that, although a single reabsorptive mechanism was concerned with the tubular transport of the amino acids studied, there was a difference in the rate of combination with some cellular component common to the reabsorption system of all the amino acids used in the investigation. Another interesting and practical aspect of amino acid excretion was reported by Eckhardt and Davidson[12]: the excretion in the urine increased little with more rapid rates of infusion of amino acid mixtures, but excretion correlated more closely with the size of the infusion. The essential amino acids seemed to be retained preferentially, whereas the other amino acids were more freely excreted in the urine. It was indicated that the increasing speed and size of intravenous mixtures of amino acids do not cause appreciable wastage in excretion, so that the body retains most of the administered amino acids for metabolic purposes. In a recent study, Kamin and Handler[13] infused various single amino acids into dogs and found a many-fold increase in the rate of excretion of other amino acids. Although the excretion of histidine and threonine was most affected, the phenomenon of increased excretion of other amino acids, when the tubules are overloaded with a specific amino acid, seems to be a general one. This work confirms the impression of competitive reabsorption by the tubules of amino acid as a phenomenon useful in explaining some of the observations noted in pathologic states in human beings.

Several possible mechanisms result in aminoaciduria. The finding may have clinical importance of greater or lesser degree depending on the mechanism operative in the specific case. Broadly speaking, there are three causes. Aminoaciduria may result from "overflow" when there are elevated blood amino acid levels. This may result from hepatic necrosis, increased protein catabolism as in wasting diseases, extensive muscular atrophies, the use of corticotrophins, hyperthyroidism, widespread cancer, extensive burns or crush injuries. Another cause of aminoaciduria with normal amino acid blood levels is renal damage or failure of tubular reabsorption. In these cases there may be concomitant evidence of renal disease, such as hematuria, pyuria, albuminuria or glycosuria. Some of the conditions in which this may occur are pyelonephritis, nephrosis, renal polyarteritis, allergic conditions of the kidney, disseminated lupus erythematosus, renal necrosis, pituitary or hypothalamic disease with polyuria, in which there is failure of reabsorption

TABLE 2. *Classification of Aminoaciduria.*

Primary:
General aminoaciduria:
deToni–Fanconi syndrome
Wilson–Uzman disease
Specific aminoaciduria:
Congenital cystinuria
Cystinosis (?)
Phenylpyruvic oligophrenia
Tyrosinosis
Secondary:
General aminoaciduria:
Hepatic insufficiency — terminal stages
Renal disease with extensive tubular damage or severe glomerular permeability defect
Toxic agents:
Chloroform
Phosphorus
Uranium
Vitamin D
Progressive muscular dystrophy
Cortisone and corticotrophic hormone therapy
Galactosemia
Diabetic ketosis
Specific aminoaciduria:
Histidinuria in pregnancy

and the necessity of maintaining the osmotic requirements of the intratubular liquid results in a high twenty-four-hour amino acid excretion, and the terminal stages of the deToni-Fanconi syndrome, in which the aminoaciduria due to disease of the renal tubules is superimposed on a primary aminoaciduria.

A third mechanism, and the most important clinically, is aminoaciduria occurring with normal blood levels of amino acid and with no demonstrable renal lesion. In some cases the aminoaciduria may be the only urinary chemical abnormality (as in hepatolenticular degeneration and cystinuria) or it may be part of other urinary chemical abnormalities (as in the deToni-Fanconi syndrome). This third mechanism is primary aminoaciduria, which requires exhaustive chemical examination of the urine to provide adequate information for differential diagnosis. In the other two mechanisms, the aminoaciduria is secondary and is of less significance since the finding constitutes an expected and necessary corollary to the existing disease for which there is ample clinical evidence. However, one should

consider the losses of amino acids thus incurred in calculating the needs in replacement therapy.

Classification of Aminoaciduria

Table 2 presents a classification of aminoaciduria that is found in various diseases or states. The division into primary and secondary is made on the basis of current knowledge. In the conditions classified as primary the aminoaciduria is believed to be a result of an etiologic factor that is usually not ascertainable. The presence of the aminoaciduria in the primary group constitutes either the only abnormality or one of the most important of the metabolic abnormalities present. What the result of prolonged aminoaciduria may be is indicated in the discussion of the specific conditions. The conditions in which secondary aminoaciduria occurs have either an endogenous cause, as in severe hepatic insufficiency, or an exogenous cause, as with the various toxic agents, which readily explains the aminoaciduria. In the general aminoacidurias, excretion of all the amino acids is increased, whereas in the specific aminoacidurias only a specific amino acid is excreted in excess, though recent studies, as in cystinuria, reveal that usually more than a single amino acid is affected even here.

deToni-Fanconi Syndrome

The deToni-Fanconi syndrome appears to be an inherited condition in which there are inborn errors of metabolism characterized by excess urinary excretion of amino acids, peptides, glucose and inorganic phosphorus.[14, 15] There is an inherent congenital defect of the tubular epithelium that apparently gives rise to the specific reabsorptive abnormalities noted. It was in the study of a case of this disease that Dent[4] applied partition chromatography with filter paper in confirming and analyzing the aminoaciduria present. Other features present in this condition are rickets or osteomalacia resistant to vitamin D therapy and elevated serum alkaline phosphatase; in some cases there is acidosis. Cirrhosis of the liver may occur with terminal hepatic insufficiency. In a few cases cystinuria with cystine renal stones and deposition of cystine in various organs has been reported. Although the aminoaciduria is general, the values of specific amino acids excreted vary from case to case. Linder[16] reported a case of the syndrome in which retinitis pigmentosa was present.

An interesting fact in the study of the aminoaciduria, glycosuria and phosphaturia is the normal or low blood values of amino acids, glucose and phosphorus. The aminoaciduria in the deToni-Fanconi syndrome is a primary type, since the blood levels are normal. It is somewhat analogous to renal glycosuria and it is quite interesting that in a case of deToni-Fanconi syndrome studied by Dent,[4] the glycosuria paralleled the levels of the aminoaciduria. A simple straight-line relation between the two was expressed by a formula. That this is unique for the deToni-Fanconi syndrome was indicated by the absence of an increase of amino acid excretion in 5 cases of typical renal glycosuria and in 1 patient who had a massive glycosuria as the result of treatment with phlorhizin. Later, Dent[17] postulated that the deaths reported after the glucose tolerance test or excess administration of glucose in the deToni-Fanconi syndrome may have been due to an acute lowering of the blood amino acids following forced aminoaciduria. This reminds one of the spontaneous falls in blood amino acids accompanying the so-called "nephrotic crisis" occuring in nephrosis, especially in children.

Peptiduria is a common feature in cases of this disease. Therefore, besides the generalized primary aminoaciduria, a great deal of amino acid is lost in the form of peptides. However, the concomitant abnormalities are also exceedingly important. The phosphaturia gives rise to a picture resembling renal rickets with osteomalacia.[18-20] The glycosuria leads to wasting, acidosis and a picture of hyperinsulism, especially in the mornings, which the patient compensates for by manifesting polyphagia. The polyuria may simulate pituitary or hypothalamic disease but can be differentiated by the abnormal ratio of peptide to amino acid in the urine, which is peculiar to the deToni-Fanconi syndrome.

The cause of the bone disease in the deToni-Fanconi syndrome is not clear, but it is postulated that the loss of the amino acids and phosphorus contributes to this deficiency. However, Dent[17] has observed cases of the syndrome with bone disease and normal serum inorganic phosphorus. Although the liver disease may occur it is not an invariable accompaniment to the condition. Dent[21] has reported cirrhosis in 3 of 10 cases studied. It is best explained on the basis of the chronic loss of amino acids, which are probably more important in the metabolic processes in the liver cells than is currently realized.[22] The inherent congenital defect of the tubular epithelium is the primary mechanism operative in the deToni-Fanconi syndrome. Although the fundamental metabolic aberrations of aminoaciduria, glycosuria and phosphaturia may cause no symptoms per se, this familial inborn error leads eventually to demineralization of the skeleton, multiple fractures, rickets and hepatic insufficiency. The course may be quite prolonged and treatment, though unsatisfactory, is restricted to orthopedic measures and medical replacement therapy whenever feasible.

Wilson-Uzman Disease

In 1912 Kinnier Wilson described a familial disease in young adults characterized by widespread involuntary movements, rigidity of the musculature and difficulty in articulation and deglutition, associated with signs or symptoms of liver disease.

The course was acute or chronic, and at autopsy the most striking features were the bilateral symmetrical degeneration of the lenticular and caudate nuclei and cirrhosis of the liver. Later, a ring of greenish-brown pigment on the under surface of the cornea near the limbus was described; this is the Kayser-Fleischer ring, which, though not always present, is believed to be pathognomonic of hepatolenticular degeneration.

The puzzling relation of this predominantly central-nervous-system disease to the liver abnormality has led to many speculations about the etiology of the syndrome. Baker,[23] in a review, summarized the various proposed theories of etiology of hepatolenticular degeneration as follows: the disease is a hereditodegenerative process affecting brain and liver; it is acquired, and the two organs are injured concomitantly by some endogenous toxin; the chief injury is to the liver, and the cerebral lesions are secondary to the liver injury; the condition is secondary to the presence of some exogenous toxin.

In the studies of hepatolenticular degeneration since its original description, elaboration of the clinical and pathological features has been the primary contribution. Absence of metabolic studies in this disease has been an obstacle to any real progress in determining its basic etiology. That impasse has been overcome by the recent finding of a generalized aminoaciduria in cases of hepatolenticular degeneration by Uzman and his associates.[24, 25] The method of partition chromatography was widely used in these studies. Rapid confirmation of this metabolic abnormality was forthcoming from the United States,[5, 26] England[22, 27] and Sweden.[28]

The older concept that the liver disease is probably primary and precedes the brain disease has had to be re-examined, in the light of present methods of studying liver disease. It is interesting that in 3 of the cases described by Wilson[23] an attack of jaundice anteceded by years the onset of cerebral symptoms. Herz and Drew[29] also report a case in which painless jaundice, fatigue and a slight elevation of temperature preceded the nervous-system symptoms by five years. In another of their cases, the patient received immunization with yellow-fever vaccine five years before the discovery of cirrhosis and the onset of the nervous-system symptoms of hepatolenticular degeneration; although this patient did not have jaundice or any other illness as a result of the yellow-fever vaccine, other members of the regiment receiving the vaccine had jaundice due to homologous serum, or inoculation, hepatitis. However, in other cases reported by these authors,[29] there were no abnormalities of liver function, even with fully developed central-nervous-system symptoms.

Similarly, Uzman and Denny-Brown[24] found in their case of hepatolenticular degeneration, in which there was massive generalized aminoaciduria, no functional abnormalities of the liver. Furthermore, a liver biopsy was not remarkable and showed no cirrhosis. In 2 other cases reported by Cooper and his associates[30] the liver biopsies gave no evidence of diffuse hepatic fibrosis or portal cirrhosis. These studies indicate that the aminoaciduria in hepatolenticular degeneration is not secondary to the liver abnormality. When aminoaciduria occurs in liver disease, it does so only because of marked hepatic insufficiency with a failure of the deamination process, which causes a marked elevation in the plasma amino acid concentration with an "overflow" type of aminoaciduria. However, in cases of hepatolenticular degeneration there is no marked elevation in the plasma concentration of amino acids.

This has led to a study of the mechanism of the aminoaciduria by Cooper and his associates[30] in patients excreting about two and a half times the normal amount of amino acids. In 6 cases of portal cirrhosis similarly studied there was no excessive excretion of amino acids. In the study of fasting plasma alpha-amino-nitrogen concentration, a range of 3.3 to 5.7 mg. per 100 cc. was found in cases of hepatolenticular degeneration compared to a range in normal patients of 3.1 to 4.7 mg. per 100 cc. It was believed that the plasma concentration of amino acids was not an important factor in the mechanism of increased renal excretion and, by exclusion, that the explanation of the urinary output of amino acids in this entity must be a disturbance in renal function, comparable to that occurring in the deToni-Fanconi syndrome. However, intravenous administration of amino acids to patients with hepatolenticular degeneration and to a group of normal subjects led to no significant differences in plasma levels or in urinary excretion in the two groups, observations that cast some doubt on the concept of a lowered renal threshold.[25]

In cases of the disease with unquestioned neurologic symptoms thus far studied, excess aminoaciduria has invariably been found, despite the occasional absence of clinical or histologic evidence of liver disease. In a family studied by Uzman and Hood[25] in which 4 of 9 siblings had died as a result of hepatolenticular degeneration, persistent aminoaciduria was found in the 5, as yet, asymptomatic siblings, no evidence of hepatic or neurologic disease being observed on intensive clinical study. The only metabolic disorder discovered was the persistent aminoaciduria. This finding has important implications since the aminoaciduria apparently occurs prior to the onset of the hepatic and neurologic disorder about which opinion regarding hepatolenticular degeneration has revolved in the past. Study of more unaffected siblings in families with Wilson's disease is clearly needed in view of the finding discussed above. Cooper and his associates[30] reported that 2 unaffected siblings of a patient with Wilson's disease had normal amino acid excretion.

It is of interest that Porter[26] did not find aminoaciduria in other neurologic diseases characterized by neuronal degeneration, particularly of a familial type. These diseases were Huntington's chorea, paralysis agitans, dystonia musculorum deformans and familial spastic paraplegia. Spillane, Keyser and Parker[27] also studied cases of Huntington's chorea, dystonia musculorum deformans and congenital choreoathetosis, and in none of these entities was aminoaciduria found. The authors suggest that the absence of aminoaciduria may be helpful in the diagnosis of doubtful cases.

At present the known facts of aminoaciduria in Wilson's disease have been summarized[25] as follows: the persistent aminoaciduria is independent of the severity of the liver abnormality since it is present even when there is no evidence of such disease; the aminoaciduria is not dependent on the amount of proteins ingested; there is no significant elevation in the blood alpha-amino-nitrogen level; there is no specificity of the pattern of amino acid excretion, since all the amino acids usually present are excreted in increased amounts with daily variations even in individual levels; and the severity of the aminoaciduria varies in individual cases without any relation to the duration of the disease except that when hepatic failure occurs a secondary aminoaciduria due to failure of deamination of amino acids is superimposed upon the pre-existent primary aminoaciduria.

It appears highly likely that the development of cirrhosis of the liver is a result of the chronic loss of amino acids,[22] an end-result also found in some cases of the deToni-Fanconi syndrome. The observation has been repeatedly made that in families in which one or more siblings had the neurologically fully developed disease, other siblings had only cirrhosis. This indicates the undoubted presence of the aminoaciduria as a primary inherited metabolic defect. Uzman and Hood[25] also recently described for the first time an excess urinary excretion of peptides with terminal dicarboxylic amino acid residues. The peptiduria may be an important link in explaining the aminoaciduria in spite of normal plasma levels since the overloading of the renal tubule with excess amounts of peptides should lead, by competitive reabsorption, to the diminution in reabsorption of amino acids, resulting in aminoaciduria.

The occurrence of degenerative lesions of the nervous system that characterizes the fully developed familiar clinical condition of hepatolenticular degeneration is not explained by the loss of amino acids. Possibly a second factor, in some way related to the metabolic disturbance responsible for the aminoaciduria, produces the central-nervous-system lesion.

In this respect, recent studies of copper metabolism in well developed clinical cases of this disease are interesting. It has long been known that copper accumulates in excess in the brain and liver.[31-33] The excretion of abnormal amounts of copper in the urine of these patients has recently been established.[26, 34, 35] This has led to therapeutic trials with BAL (2,3-dimercaptopropanol) in the effort to eliminate copper from the tissues of these patients by increasing the urinary excretion of copper.[27, 33, 36, 37] Although the results have been encouraging, startling improvement has not been noted. The relation, if any, between the observed aminoaciduria and excess copper excretion has to date found no adequate explanation. Since the aminoaciduria probably does not explain the nervous-system changes, one may postulate a more generalized metabolic disturbance or invoke a secondary metabolic factor, which superimposed on the aminoaciduria, preceding and accompanying the disease, produces the classic picture of hepatolenticular degeneration. The secondary factor may be the defect in handling dicarboxylic amino acid peptides recently described.[25] It is not improbable that the accumulation of copper in the tissues of these patients is the result of a complex formation between these peptide residues accumulating in tissues as a consequence of this metabolic defect and their known affinities to bind copper.

In the light of these recent findings, reconsideration of the nomenclature applied to this heredofamilial disease appears necessary. What has been called Wilson's disease, or hepatolenticular degeneration, is apparently the end-product of a chronic metabolic disorder. The abnormality — the aminoaciduria — certainly precedes the hepatic disease, probably giving rise to it. The hepatic condition actually may remain without a neurologic component. The aminoaciduria thus appears more familial than the disease as described by Wilson. In the family in which hepatolenticular degeneration appears, what about the sibling who has aminoaciduria but no liver or neurologic abnormality? Certainly, he is not completely healthy, and potentially he may become cirrhotic, or hepatolenticular degeneration, the usual connotation of Wilson's disease, may develop. Thus, this sibling with the sole defect of aminoaciduria cannot be considered to have Wilson's disease, since Wilson never described this eventuality, nor can a diagnosis of hepatolenticular degeneration be made in the absence of liver or central-nervous-system symptoms and disease. Although eponyms, particularly hyphenated ones, are distasteful to many members of the medical profession, it appears that, in the absence of an etiologic factor to explain the disorder of amino acid metabolism encountered, the altered nomenclature of Wilson–Uzman disease would broaden the concept of the condition to include the newly discovered metabolic nature of this disorder, and the apparent primacy of the metabolic factor in its hereditary pattern.

Cystinuria and Cystinosis

Cystinuria is an inborn error of metabolism in which cystine is excreted in excess. The normal excretion of cystine is usually less than 100 mg. per

twenty-four hours, whereas in cystinuria as much as 1.0 gm. may be excreted. Since cystine is one of the most insoluble of the amino acids, crystals and calculi may form. That this disease is not entirely confined to the abnormal excretion of cystine is suggested by Yeh and his associates,[38] who reported that other amino acids were excreted abnormally in a patient with cystinuria; there was also an increase in excretion of arginine and lysine, with a decrease in glycine and histidine. Stein[39] has also confirmed the finding of excessive amino acids, other than cystine, in this condition. This indicates that in cystinuria the metabolism of amino acids may be deranged in several respects. It is interesting to note again that, in some cases of the deToni-Fanconi syndrome, the clinical findings of cystinuria, with renal lithiasis, may occur. It has not yet been reported in Wilson-Uzman disease although that possibility seems likely in view of the excess cystine excreted.

Dent and Rose[40] have recently comprehensively studied this subject and make a distinction between two varieties of disorder in the metabolism of cystine. Cystinosis is a condition manifested by widespread deposition of cystine crystals in many body tissues, including the liver and kidney. There is an apparent generalized enzymatic defect in which there may or may not be increased cystine excretion in the urine. Clinically, it is an invariably fatal condition at an early age.

On the other hand, in cystinuria the amino acid metabolism is normal so far as the liver and body tissues are concerned. The patient with cystinuria is clinically indistinguishable from a normal person, but as a result of an inherited defect of the renal tubules he can only reabsorb from the glomerular filtrate small proportions of cystine, lysine and arginine. These substances are therefore concentrated many times in the urine. Since cystine is insoluble, under proper circumstances but not in all cases of cystinuria, renal calculi may form and predispose to the sequelae of any renal stone. Thus, cystinuria is clinically defined as the continuous excessive excretion in the urine of cystine, lysine and usually arginine in the presence of normal plasma levels of these and all other amino acids. It is a hereditary condition, present from birth, and consistent with normal health aside from the tendency to form renal calculi. The significance of concomitant excretion of other amino acids should be considered in the light of the competitive reabsorption phenomenon mentioned above.

Phenylpyruvic Oligophrenia and Tyrosinosis

As Galdston[41] graphically demonstrated, alkaptonuria is but one of three known disturbances in the metabolism of the amino acids phenylalanine and tyrosine. In alkaptonuria, a rare disease in which there is an inherited recessive trait at birth, homogentisic acid is the only abnormal substance excreted in the urine. Strictly speaking, alkaptonuria is not an aminoaciduria because homogentisic acid is not an amino acid. However, since homogentisic acid is an intermediate metabolite in the catabolism of tyrosine and phenylalanine, two amino acids, it is a disorder of amino acid metabolism and included for explanatory purposes. In cases of alkaptonuria homogentisic acid is constantly excreted in the urine, whereas in normal patients it is not, even when it has been administered. The amount excreted is increased by ingestion of either tyrosine or phenylalanine. Urine containing homogentisic acid turns brown or black if the specimen is alkaline or when it is exposed to the air. Alkaptonuric urine reduces Benedict's solution but is differentiated from glucose by its failure to undergo fermentation with yeast and by its lack of optical activity. Occasionally, an erroneous diagnosis of diabetes mellitus may be made. Clinically, despite excretion of homogentisic acid from birth, the disease makes itself known in the second or third decade, when ochronosis develops. This is a pathologic deposition of black pigment, a polymer of homogentisic acid, in cartilages, fibrous tissue, tendons and atheromatous areas. It is manifested by a pigment in the sclera on either side of the corneal limbus varying from brown to slate gray and by a bluish discoloration of the ears. A deforming arthritis involving the large joints and spine is the most common clinical manifestation, but that the disease is consistent with long life is shown by the study of an alkaptonuric patient who was ninety-four years old.[41]

In phenylpyruvic oligophrenia there is a disturbance in the metabolism of phenylalanine leading to the urinary excretion of phenylpyruvic and phenylacetic acids, which are not excreted in the normal patient. The defect is in the reactions by which phenylalanine is converted to tyrosine. There is usually an increased blood concentration of phenylalanine, which, because of apparent incomplete deamination, leads to the excretion of the abnormal compounds. It appears that one or more enzymes, which enable the amino acid phenylalanine to be used by the body, are absent in this disease. Cantor[42] reported a case in which chromatographic study of the urine had been performed. In addition to phenylalanine, aspartic acid, glycine, tyrosine, alanine and proline were found to be present. Apparently, here again, more than one amino acid is excreted. The disease, which is transmitted by a single autosomal recessive gene, is characterized by marked mental retardation, and often extrapyramidal manifestations such as athetosis and exaggerated tendon reflexes. The people affected are usually blue-eyed blondes with physical attractiveness and a susceptibility to eczema as frequent concomitant findings. It is estimated that less than 1 per cent of all feeble-minded institutionalized patients have phenylpyruvic oligophrenia.

Only 1 case of tyrosinosis has been reported. It is caused by the inability to oxidize a derivative of tyrosine, p-hydroxyphenylpyruvic acid, which is excreted in the urine. Apparently, the defect has little clinical significance.

Aminoaciduria in Liver Disease

Deamination of amino acids primarily occurs in the liver and is one of its functions fundamental to survival. It is therefore preserved as long as possible, failing only in severe hepatic insufficiency, as Lichtman[43] has reported. When deamination fails, there is increased concentration of amino acids in the blood with a relatively proportional aminoaciduria. Kirk[44] compared the excretion of amino acids in groups of normal patients and patients with liver disease. In acute hepatitis, cirrhosis and obstructive jaundice, without demonstrable renal lesions, the excretion of amino acids, both in the fasting state and after ingestion of 25 gm. of glycine, did not differ significantly from that of the normal patients. Eckhardt and his associates,[5] in a study of the urinary excretion of amino acids in 7 patients with severe liver disease (5 cases of cirrhosis, and 1 each of hemochromatosis and subacute yellow atrophy), reported no significant difference from the values in normal patients. They also found that the excretion after infusion of amino acid mixtures was similar to that noted in normal patients. It was concluded that intravenously administered amino acids were well tolerated by patients with severe liver disease and were metabolized and excreted in a manner differing little from normal.

Only in acute yellow atrophy and terminal liver disease, in which there is necrosis and autolysis of hepatic tissue, is aminoaciduria invariably present. The occasional finding of leucine and tyrosine crystals in the urine is believed to be mainly due to autolysis, although at this terminal stage of liver disease there is also increased amino acid concentration of blood, because of failing deamination function, with consequent overflow aminoaciduria. These findings tend to substantiate the belief, expressed above, that the aminoaciduria in Wilson–Uzman disease is not explained, in most cases, by the degree of impairment of liver function present.

The most recent study of amino acid metabolism in liver disease utilized urinary chromatographic findings in a large group of patients.[45] The previous studies were largely confirmed, but in addition there appeared to be certain patterns of amino acid excretion in various types of liver disease. Even in mild cases of liver injury, abnormalities in the metabolism of one or more amino acids were sometimes found, increasing with the severity of the disease to the grossly abnormal patterns and concentrations involving many amino acids and lasting for long periods that are found in the severe hepatic necrosis of acute yellow atrophy. Thus, several patterns of aminoaciduria were found. The first (already mentioned), which occurred in acute liver failure, was a gross excess of all the common amino acids; the second, consisting of an excess of many amino acids with a slight rise in concentration, was found in acute infectious hepatitis; and the third, an excess of cystine, alone or together with other amino acids, was observed in chronic liver disease and infiltrations of the liver. Other patterns were suspected.

In a detailed study of hepatic coma, utilizing chromatographic urinary amino acid data, Walshe[46] confirmed the gross abnormality in amino acid excretion in this condition. The plasma alpha-amino-nitrogen was also raised in these cases, differentiating this "overflow" type of aminoaciduria from that found in the deToni-Fanconi syndrome, Wilson–Uzman disease and cystinuria. On the basis of these abnormalities in amino acid metabolism and the neurologic and mental aberrations found in hepatic coma, Walshe suggested that the neurologic syndrome of hepatic failure may be caused by a disturbance of the metabolism of one or more amino acids following a breakdown of the liver mechanism for regulating the plasma amino acid levels and the liberation of potentially toxic amounts of certain amino acids and peptide compounds from the autolysing liver. That determinations of the level of alpha-amino-nitrogen in the plasma may not demonstrate such disturbances is seen in the fact that considerable variations in the pattern of blood amino acids and of urinary amino acid excretion may occur with no significant change in the plasma alpha-amino-nitrogen concentration. Since varying patterns of amino acid excretion have been noted in the study of individual cases of hepatic coma, presumably the abnormalities of brain metabolism may vary. Moreover, in some cases, hepatic coma is reversible. The hypothesis, that changes in the amino acid pattern of body fluids are capable of producing varying neurologic syndromes, which would be potentially reversible and not associated with histologic changes in the brain, is extremely interesting. Further study is required to confirm the validity of this supposition, which brings into focus inquiry regarding the connection of the disturbance of amino metabolism found in other disorders, already reviewed, and their central-nervous-system manifestations.

Toxic Agents Causing Aminoaciduria

In terminal chloroform and phosphorus poisoning aminoaciduria has been described.[2] A most timely and valuable study by Rothstein and Berke[47] reports a diagnostic test for uranium poisoning based on the finding of aminoaciduria. Uranium is a potent nephrotoxic agent affecting primarily the proximal convoluted tubule. The marked aminoaciduria occurs despite the maintenance of normal blood concentration of amino acids, similar to the

findings in the deToni-Fanconi syndrome and Wilson–Uzman disease.

A most interesting case was reported by Van Creveld and Arons.[48] Large dosages of vitamin D had been given for a year to a child of seventeen months, leading to the development of rickets and aminoaciduria. The authors believed that this was caused by the effect of the vitamin D on the kidney tubule, causing in effect a transitory deToni–Fanconi syndrome. Cessation of the vitamin D therapy, to which the child was considered hypersensitive, led to alleviation of the condition described.

Recently, Spencer and Franglen[49] reported gross aminoaciduria in a patient who suffered an extensive lysol burn. There was azotemia and anuria for ten days, resulting in a blood urea nitrogen of 474 mg. per 100 cc. During the early diuretic phase of recovery, gross tubular dysfunction, similar to that described in other toxic nephroses, was noted. There was massive aminoaciduria with a normal alpha-amino-nitrogen plasma concentration for the first two days of the diuretic period. Thereafter, the urinary amino acids were not remarkable. The authors believe that poisoning with heavy inorganic metals resulting in acute renal lesions will also demonstrate aminoaciduria.

Miscellaneous Secondary Aminoacidurias

Ames and Risley[50] studied 32 urine specimens from patients with various types of progressive muscular dystrophy by partition chromatography and found a generalized aminoaciduria. The excessive creatinuria in these patients has been well known, owing to the muscle wasting, which is probably also the source of the aminoaciduria. However, because of the known competition offered by creatine to the tubular reabsorption of amino acids,[11] one may ascribe part of the aminoaciduria observed directly to the excessive creatinuria rather than to the destruction of muscle protein. Early cases did not show as marked an excretion of amino acids as late cases. The types studied included the pseudohypertrophic and fascioscapulohumeral types and amyotonia congenita.

Of current interest is the report of Brodie and his associates[51] of an increase in the urinary excretion of certain amino acids during the administration of adrenocorticotrophic hormone and cortisone to patients with rheumatoid arthritis. The cause of the increased excretion is not known and may or may not be associated with the metabolic changes brought about by the remission of the arthritis. In this respect, the experimental findings of Friedberg and Greenberg[52] are of interest since it was shown that hypophysectomy, adrenalectomy and thyroidectomy decreased the blood amino acid level, whereas thyroxine and adrenocortical extract increased it. Apparently, future studies of the relation of the endocrine glands to amino acid metabolism may be a fruitful area of investigation.

Recently Holzel, Komrower and Wilson[53] reported marked aminoaciduria in 2 cases of galactosemia. It was of interest that on a milk-free diet the gross aminoaciduria tended to revert to a normal pattern, studied by partition chromatography. It is probable that this was another case of aminoaciduria secondary to competitive reabsorption at the renal tubular level, although the authors speculate that the aminoaciduria may be specific for galactosemia with a specific renal mechanism.

The urine of pregnant women contains more histidine than that of nonpregnant subjects, but this is of no diagnostic import because of the variability of urinary histidine in both pregnant and nonpregnant women.[2] Altered renal threshold or impairment of an enzymatic metabolic activity in the liver during pregnancy is among the theories presented to explain the histidinuria, which decreases immediately after parturition. Another explanation is that the excess excretion of steroids and other hormones by the pregnant woman may, by overloading the renal tubule, lead to competitive reabsorption, with failure to reabsorb histidine normally.

Summary

A review of the clinical significance and a classification of aminoaciduria is presented. In view of the introduction of partition chromatography in clinical investigations, it is highly probable that the horizons of the knowledge of amino acid metabolism will widen.

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MEDICAL INTELLIGENCE

FATAL ANAPHYLACTIC SHOCK FROM PROCAINE PENICILLIN*

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REACTIONS following the administration of penicillin in its various forms are quite common, being reported in 5 to 10 per cent of all patients receiving this drug.[1] The vast majority of these reactions are fortunately minor, rarely being severe enough to require discontinuance of the drug. The potentially antigenic properties of penicillin have been pointed out many times, and the occurrence of serious anaphylactic reactions was predicted by many early observers.[2] Considering the wide use of penicillin in its various modes of administration, the number of anaphylactic reactions reported in the literature is astonishingly small (Table 1). Of the 2 previously reported fatal cases of anaphylactic reactions following the use of penicillin, 1 was a delayed reaction occurring in a debilitated postoperative patient[4] and cannot be classified with the immediate overwhelming reaction of the type occurring in the case reported below. The second fatal case, reported by Waldbott,[6] occurred in a patient with severe bronchial asthma who died almost immediately after the (supposedly intramuscular) injection of 50,000 units of penicillin. The drug was administered by a relative in the home, and no autopsy was done. However, the type of immediate reaction and death within a few minutes as described is typical of anaphylactic shock. So far as one can tell from a review of the literature, the case reported below is the first of an immediately fatal anaphylactic shock after the administration of penicillin in any form in which a physician was present to observe the reaction and in which an autopsy was performed. Several severe, immediate, nonfatal anaphylactic reactions have

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followed parenteral as well as topical administration of penicillin.[5, 7, 8]

Reactions to penicillin can generally be classified as of two main types; urticarial, serum-sickness-like reactions or erythematovesicular eruptions.[9] The first type usually appears three to ten days after administration of the drug has been discontinued and consists of malaise and fever, urticaria and arthralgia, often with serous joint effusions and exfoliative dermatitis. The second type is much less severe, and is usually confined to a generalized erythematovesicular eruption.

A third type, which is fortunately extremely rare, is immediate anaphylactic shock. This reaction has been induced in man by heterologous serum, by liver extract, arsenicals, tetanus toxoid and other therapeutic and prophylactic preparations containing antigenic materials. The understanding of this type of reaction in man is largely based on knowledge of experimental anaphylaxis in animals, the best animal for this purpose being the guinea pig.[10] If 0.1 to 1.0 cc. of horse serum is injected into a normal guinea pig, there is no visible effect. However, this injection induces a state of sensitization in the animal, and if a similar injection is given seven to ten days later, there is an immediate, violent reaction characterized by restlessness, labored respirations and convulsions, usually causing death within a few minutes. Such a sensitization has been produced by as little as 0.009001 cc. of horse serum, and a state of sensitization may be shown to persist for as long as two years. There is a high degree of specificity among different species, each animal reacting in much the same way regardless of the type of antigen used, although in man, the various types of allergic response to any specific antigen varies considerably. In the guinea pig the outstanding manifestation of anaphylactic shock is bronchospasm, which produces death by asphyxia, whereas in the rabbit, circulatory failure due to spasm of the pulmonary vessels that prevents the passage of blood from the right to the left side of the heart is the principal manifestation. Although the outward symptoms vary considerably in different species, the chief manifestations seem to be due to spasm of smooth muscle and increased capillary permeability.

That penicillin can cause anaphylactic sensitization has been well demonstrated in the laboratory by McClosky and Smith[11] and others. These workers gave daily subcutaneous and intraperitoneal injections of penicillin to guinea pigs, subsequently producing anaphylactic shock by intravenous or intracardiac injections after an adequate incubation period. Tests on the isolated uterus by the Schultz-Dale technic have also demonstrated that sensitization can be produced by penicillin. As pointed out by Cormia, Jacobson and Smith,[3] many patients with anaphylactic reactions have not previously had penicillin. These authors show that such patients usually have a history of previous dermatophytosis, and postulate cross reactions with the common trichophytes. They were able to demonstrate such cross antigenicity experimentally.

TABLE 1. *Previously Reported Anaphylactic Reactions to Penicillin.*

AUTHOR	YEAR	DOSAGE	ONSET OF REACTION	HISTORY OF ALLERGY	PREVIOUS PENICILLIN THERAPY	COMMENT
Cormia et al.[3]	1945	20,000 units of crystalline penicillin intramuscularly	10 minutes after injection	No	No	Rapid recovery without specific treatment
Wilensky[4]	1946	Multiple dosage of crystalline penicillin	26 days after injection	No	No	Not true anaphylactic shock; patient died.
O'Donovan and Klorfajn[5]	1946	15,000 units of sodium penicillin intramuscularly	15 minutes after injection	Yes	Yes (spray)	Recovery in 2 days
Waldbott[6]	1949	50,000 units of crystalline penicillin intramuscularly	Within 5 seconds	Yes (asthma)	Yes	Death in few minutes
Burleson[7]	1950	200,000 units of procaine penicillin G, with 0.5 cc. of 1 per cent procaine, intramuscularly	15–20 minutes after injection	No	Yes	Recovery after intravenous injection of diphenhydramine
Everett[8]	1951	30,000 units of crystalline penicillin G with ephedrine	"Almost immediately"	No	Yes	Local instillation into maxillary antrum; recovery in 2 hours; 3 months later patient received 300,000 units of procaine penicillin G in oil followed by severe anaphylactic shock in 15 minutes.
Everett[8]	1951	30,000 units of crystalline penicillin G with ephedrine	"Within few seconds"	Yes (asthma)	Yes	Local instillation into maxillary antrum; recovery in 1 hour; reaction not true anaphylactic shock.

CASE REPORT

E. C. B., a 57-year-old laborer, entered the hospital on April 7, 1952, for excision of a tender lump in the right breast, which had been enlarging for the past 3 months.

There were no other complaints, and he had been in good general health.

The past history revealed previous hospitalization here in October, 1949, when an epigastric hernia had been repaired under local (procaine) anesthesia. The patient was hospitalized here again 1 year later, for the treatment of multiple fractures and lacerations following a motorcycle accident; during this hospitalization he received penicillin procaine and manifested no sensitivity to the drug. System review was negative. No familial or personal history of allergic phenomena was elicited.

Physical examination revealed a well developed man who appeared to be in good health. The blood pressure was 115/65, and the pulse 80, with a regular rhythm. The chest was slightly emphysematous; there was a dorsal kyphosis. The lungs were clear to auscultation and percussion, no rales being heard on normal respiration or forced expiration. The remainder of the physical examination was within normal limits except for the right breast, which showed a 2-cm. tumor underlying the areola. No lymphadenopathy could be detected. Laboratory work, including urinalysis, serologic test and blood counts were within normal limits, with no eosinophils in the differential blood count. X-ray study of the chest showed no significant abnormalities.

On the day after admission under Pentothal Sodium anesthesia, a small nodule was removed from the right breast, the operative procedure taking 15 minutes. The patient was up and walking about the ward by noon, eating the regular noon and evening meals. At 9:25 p.m. an intramuscular injection of 300,000 units of procaine penicillin G was given by the ward nurse, who observed no return of blood on a routine attempt to withdraw the syringe plunger prior to injection. (This was the first dosage of penicillin received on this hospital admission, and 4 other patients had received similar injections from the same vial.) The patient was sitting on the edge of the bed conversing with the other patients and the nurse. Approximately 1½ minutes later he suddenly became cyanotic and coughed, and a tonic muscular spasm developed. He was seen by the surgical resident within 30 seconds of the onset of symptoms. At this time the respirations were gasping, cyanosis was extreme, the blood pressure was unobtainable, and the pulse weak and thready. Atropine sulfate, 0.6 mg. (1/100 gr.), was given intravenously, and positive-pressure artificial respiration was started with a breathing bag, but expansion of the chest was poor. The entire picture was so suggestive of respiratory obstruction that direct laryngoscopy was immediately done. The vocal cords were found to be widely abducted, with no evidence of obstruction to the upper respiratory passage. Positive-pressure artificial respiration was continued. Aminophylline, 0.5 gm., was given intravenously, and 1 cc. of 1:1000 solution of epinephrine was instilled within the heart. The patient showed little change, however, and after a few abortive diaphragmatic respiratory efforts died at 9:35 p.m., 10 minutes after administration of the penicillin.

Complete post-mortem examination revealed no gross anatomic abnormalities except for increased mucus in the tracheobronchial tree. Microscopical studies of the tissues likewise showed absolutely no pathologic changes to account for the patient's death. Microscopical diagnosis of the surgical specimen was gynecomastia.

Discussion

This case is typical of acute fatal anaphylactic shock produced by procaine penicillin G in a person highly sensitized to this drug. The rapidity of onset and severity of the reaction make it probable that the injection was inadvertently given intravenously, although the usual precaution of attempting to withdraw the syringe plunger was taken. Regrettably, no blood sample was obtained for post-mortem antibody studies; however, the nature of the reaction in addition to the absence of any positive findings at autopsy, leaves no doubt that this was a case of true anaphylactic shock. The absence of a history of allergy, as well as the previous administration of procaine penicillin to this patient without incident, indicates these factors to be of little help in predicting the presence of a high degree of sensitivity. Consequently, and in spite of the extreme rarity of this type of reaction, the indiscriminate use of penicillin should be avoided. In patients with a history of previous reaction, use of another penicillin (such as penicillin O) or one of the other antibacterial drugs seems indicated. Routine skin testing is not possible because of the vast usage of penicillin. Diphenhydramine hydrochloride administered intravenously is probably the preferred treatment in anaphylactic reactions.

Summary

A case of fatal anaphylactic shock following the administration of 300,000 units of procaine penicillin G is presented, along with a brief review of previous similar case reports.

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PHYSICIAN ORATORS OF BOSTON

James F. Ballard*

BOSTON

THE Boston Massacre occurred in 1770 and it became the custom of the Town to commemorate the event by having a distinguished person deliver an oration on March 3 of each year. The first fifteen orations concerned this famous event. In 1783 the anniversary of the massacre was abolished, and Independence Day was officially designated as the Fourth of July, after which orations were delivered on this anniversary. An interesting book on the various orators was written in 1854 by James Spear Loring.† Many noted Boston physicians, from the beginning, delivered a number of the commemorative addresses.

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†Loring, J. S. *The hundred Boston orators appointed by the municipal authorities and other public bodies from 1770 to 1852; comprising historical gleanings, illustrating the principles and progress of our republican institutions.* 720 pp. Boston: John R. Jewett and Company, 1854.

The first, in 1771, was by Dr. Thomas Young. He was followed by Dr. Joseph Warren, of Bunker Hill fame, who delivered the orations of 1772 and 1775. In 1773 the orator was Dr. Benjamin Church, who, at the time of the massacre, was a surgeon in the British army and who examined the body of Crispus Atticks, one of the victims of the massacre. His oration of 1773, at an adjourned town meeting, attracted so many people that the moderator, John Hancock, and the orator had to be taken into the meeting through a window.

In 1774 Church was a member of the Provincial Congress and physician general to the patriot army. In 1772 he became the first Grand Master of the Rising Sun Lodge of Masons. In 1775 he was director-general of the hospital in Boston and in the same year was charged with treason by General Washington, tried by court-martial, convicted and sent to prison. He was released from his imprisonment in Norwich, Connecticut, in May, 1776, and set sail for London or the West Indies, and was never heard from again. According to a family tradition, the ship on which he sailed was wrecked at sea and all on board perished.

In 1783 Dr. Thomas Welch spoke on the massacre, and Dr. John Warren, brother of Joseph Warren, spoke on national independence. Dr. Warren had the honor of delivering the first oration on the new anniversary, Independence Day, the Fourth of July.

In 1804 the orator was Dr. Thomas Danforth, and in 1835, it was Dr. Jerome van Crowninshield Smith. Dr. Smith was a man of many interests: in 1826 he was port physician of Boston; in 1837 and 1848 he was elected to the State Legislature, and in 1854 was mayor of Boston. He was an advocate, with considerable success, of public-health matters and was especially interested in obtaining pure water for his city. He founded and edited, from 1823 to 1828, the *Boston Medical Intelligencer*, and later edited the *Boston Medical and Surgical Journal*, a consolidation of various periodicals, from 1835 to 1857. He also wrote on various subjects, medical and nonmedical, and was the editor of the *Boston Weekly News Letter* (1825–1826).

In 1787 Dr. John Brooks delivered the oration for the Massachusetts branch of the Society of the Cincinnati. Dr. Brooks had been apprenticed to Dr. Simon Tufts, brother of Dr. Cotton Tufts, from the early age of fourteen years to twenty-one. He practiced his profession and became an officer in the Minute Men, finally attaining the rank of colonel. He was commander of the Ancient and Honorable Artillery Company of Boston in 1786, and was major-general of the Massachusetts troops in Shay's rebellion. He later became adjutant-general and Governor of Massachusetts (1816–1823). He was president of the Massachusetts Medical Society from 1823 to 1825. He was an ardent patriot, and according to his pastor, Andrew Bigelow, "an estimable man."

The book reads like a Boston hall of fame, including such noted figures as John Hancock, Peter Thacher, Thomas Dawes, John Quincy Adams, Robert Treat Paine, Daniel Webster, William Lloyd Garrison, Rufus Choate, Horace Mann, Charles Francis Adams, and Charles Sumner.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38-1931

PRESENTATION OF CASE

A sixty-seven-year-old woman was admitted to the hospital because of abdominal pain and mental confusion.

Four weeks before admission, after a period of severe constipation, right-upper-quadrant pain, which radiated around into the back and which was accompanied by occasional vomiting, developed. She was admitted to another hospital and after an enema apparently felt much improved; however, while in the hospital she was thought to be slightly jaundiced, and a Graham test showed a nonfunctioning gall bladder. An abdominal laparotomy was performed, and the gall bladder was found to be normal and the liver to be slightly smaller and slightly rougher than normal; pathological examination of a liver biopsy was reported as showing "either a nodular regenerative hyperplasia of liver or a primary adenoma (hepatoma) of liver cells." On the day after operation the skin and scleras were definitely yellow, and within two days she was deeply jaundiced; this gradually subsided over the next three weeks. She allegedly felt quite well postoperatively and was discharged after two weeks. On returning home she complained of feeling weak and tired and of midepigastric pain, which occurred immediately after eating; she had occasional bouts of vomiting, also associated with food intake. One week prior to entry the abdominal pain was so severe that she refrained from eating altogether. Five days before entry the pain became so severe that she

was given injections of morphine and atropine for relief, and during the next three days she received four such injections. Four days before admission the abdomen was swollen, and she was passing "black sticky" stools. One day before admission she began to have diarrhea, with sixteen bowel movements that day. She took eight doses of a mixture of powdered opium, bismuth subnitrate and calcium carbonate, after which the diarrhea ceased. Three hours after the second dose she became disoriented; throughout the day the disorientation became more marked.

She had suffered from constipation most of her life, and one and a half years before admission, after severe constipation lasting several weeks, abdominal pain and gaseous distention developed. She was admitted to another hospital, was given enemas that released a fecal impaction and was completely relieved of pain. From then until the onset of this illness she had continued to be constipated as usual and to take frequent laxatives. Prior to the onset of this illness she had had a good appetite, had maintained her weight and strength and had not had any other gastrointestinal symptoms. In the four weeks before admission she had allegedly lost a great deal of weight. There were no known serious illnesses in the past.

Physical examination revealed an obese, semistuporous woman who appeared to be chronically ill and dehydrated and who was able to respond to simple commands only. There was a suggestion of mild icterus of the skin and scleras. There were a few spider telangiectases over the upper chest. There were a few moist rales at both lung bases. The heart appeared to be slightly enlarged, and there was a loud, blowing, Grade IV systolic murmur heard best at the base of the heart. The abdomen was protuberant and tympanitic, with dullness in the flanks. A faint fluid wave was present. The abdomen was diffusely tender to palpation — most noticeably on the right side. There was no definite spasm and no palpable organs or masses. Pelvic and rectal examinations were negative, as was neurologic examination.

The temperature was 99.8°F., the pulse 100, and the respirations 28. The blood pressure was 130 systolic, 84 diastolic.

The urine had a specific gravity of 1.022 and was normal. Examination of the blood showed a hemoglobin of 15 gm. and a white-cell count of 13,500, with 92 per cent neutrophils. The nonprotein nitrogen was 32 mg., the total protein 6.86 gm., the albumin 3.17 gm., the globulin 3.69 gm., the serum bilirubin 0.8 mg. direct and 1.5 mg. total, the alkaline phosphatase 3.6 units and the serum amylase 10 units per 100 cc.; the sodium was 134.7 milliequiv., and the potassium 3.5 milliequiv. per liter. Spectrographic examination of a blood sample was negative for methemoglobin. The prothrombin time was 15 seconds (normal, 13 seconds). The stool gave a ++++ guaiac reaction. Sigmoidoscopic examination was negative. A two-hour test for urine urobilinogen demonstrated 5.6 Ehrlich units. Roentgenograms of the chest showed the diaphragm to be elevated bilaterally, with some atelectasis in the lower lung fields; the heart was prominent in the region of the left ventricle, and the aorta moderately tortuous. Films of the abdomen revealed gas in multiple loops of small bowel, which were moderately distended, very little if any gas in the colon, some contrast substance in loops of bowel, possibly small bowel, and the absence of distinct visceral outlines suggesting peritoneal fluid. At barium-enema examination owing to the patient's physical condition the colon could be filled only to the hepatic flexure; no abnormality was noted in the part of the bowel that could be examined. An electrocardiogram showed a sinus tachycardia at a rate of 105, a PR interval of 0.14 second, a QRS interval of 0.08 second, normal voltage and axis, and nonspecific ST-segment and T-wave changes. Abdominal paracentesis yielded cloudy, straw-colored fluid, which contained 13,800 red cells and 10,400 white cells per cubic millimeter, of which 84 per cent were neutrophils. The fluid contained 3.7 gm. per 100 cc. of protein and 9 units per 100 cc. of amylase. Cultures of the fluid showed no growth on blood agar, with alpha-hemolytic streptococcus and a few colonies of *Escherichia coli* in thioglycolate broth. A blood culture demonstrated no growth.

A Miller–Abbott tube was passed. The patient was given intravenous therapy, blood transfusions and antibiotics. She continued to complain of severe abdominal pain and became more and more disoriented and confused. Her abdomen became more protuberant; peristalsis became definitely diminished. The tenderness persisted, and rebound tenderness developed but still no spasm occurred. There was no diarrhea after entry to the hospital; enemas had good results. On the second day the temperature was 100°F., the pulse 120, and the white-cell count 25,500, with 98 per cent neutrophils, of which 1 per cent were myelocytes; 1 per cent of the red cells were nucleated. X-ray films of the abdomen showed the extremity of the Miller–Abbott tube to lie in the third portion of the duodenum and the opaque substance previously noted to have advanced into the colon; there were fewer distended small-bowel loops, but there was still one gas-distended loop in the region of the terminal ileum. The patient seemed to improve somewhat on the third day. The temperature was 99°F., the pulse 110, and the white-cell count 20,350, with 80 per cent neutrophils; aspirated material from the Miller–Abbott tube gave a ++++ guaiac reaction. She continued to have diffuse abdominal tenderness that became most marked with a suggestion of a mass and spasm on the left side and with an absence of peristalsis. A lumbar puncture showed normal dynamics and a clear spinal fluid under a pressure

equivalent to 76 mm. of water; the fluid gave a negative Pandy reaction and contained 11 red cells and 5 white cells per cubic millimeter. On the fourth day she deteriorated markedly; the urinary output dropped to 0, the temperature rose to 101°F., and the blood pressure became unobtainable. X-ray films of the abdomen showed considerable gaseous distention of the stomach with the tip of the tube in the fundus; gas was also observed in several small-bowel loops on the right.

She died early on the fifth day.

Differential Diagnosis

Dr. Charles L. Short*: May I see the x-ray films?

Dr. James J. McCort: The chest films obtained on admission show bilateral elevation of both leaves of the diaphragm. There is a small amount of basal atelectasis owing to the high position of the diaphragm. The heart is not grossly enlarged but lies transversely because of the high diaphragm. There is tortuosity of the aorta. No fluid is seen in the pleural cavity.

Plain films of the abdomen obtained at the same time show symmetrically dilated loops of small bowel. There is an opaque substance within the loops of small bowel that might be due to the bismuth subnitrate and calcium carbonate, which the patient had taken twenty-four hours prior to examination. A barium enema was unsuccessful; the barium passed only as far as the hepatic flexure. The visualized portion of the colon shows no intrinsic abnormality, but there is evidence of extrinsic pressure on the rectum and rectosigmoid. The most common cause of such pressure is a tumor of the pelvis although the same appearance can be produced by ascites. The loss of visceral outlines and the properitoneal fat line is also evidence of increased peritoneal fluid. The film obtained on the fourth day shows only a small amount of gas in the right side of the colon. The film obtained on the last hospital day shows a markedly dilated stomach and a slightly dilated loop of small bowel in the right side of the abdomen.

Dr. Short: Would you say that she had ileus?

Dr. McCort: I think the appearance of the abdominal film on admission is that of ileus with a large amount of peritoneal fluid.

Dr. Short: As time went on, did the ileus improve or remain the same?

Dr. McCort: I think it improved. The distention of small bowel is less marked.

Dr. Short: There is no way of determining the site of the ileus or of demonstrating a point of obstruction?

Dr. McCort: I cannot see a definite point of obstruction.

Dr. Short: There is no free air?

Dr. McCort: No.

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Dr. Short: Are you able to see the liver?

Dr. McCort: On the last abdominal film I believe the liver edge can be made out below the costal margin, but I am not sure of it.

Dr. Short: The patient had, in effect, a gastrointestinal series with the bismuth she took at home. The bismuth seems to have moved as far as the colon, so there was not complete obstruction?

Dr. McCort: Certainly, there is no obstruction above the colon.

Dr. Short: She had no methemoglobinemia after she came into the hospital so I do not believe that the medication given her before admission had anything to do with the terminal illness — she did not receive enough to affect her systemically.

On first reading of this case history it seemed that an unusual amount of information was presented to the discusser. He was given not only the findings at the laparotomy five weeks before the death of the patient but also the report of a liver biopsy at that time. The biopsy report is not too helpful, but of course if it were conclusive and definite there would be no reason to have this exercise. From the inconclusive nature of the biopsy report, it seems evident that I shall have to make a diagnosis on the clinical and laboratory evidence that is at hand.

I should like to start by attempting to answer the question whether or not the patient had liver disease of sufficient severity to be connected directly with the cause of death. At autopsy it is not uncommon to find portal cirrhosis that caused few symptoms during life and had nothing to do with the final illness. In this case I think there is inescapable evidence that the patient had severe liver disease. What are the points that favor that conclusion? She was definitely jaundiced, according to the history. In the hospital the equivocal statement was made that there was "a suggestion of mild icterus." More helpful, perhaps, is the notation that the quantitative bilirubin test was slightly elevated. The spider telangiectases constitute an important finding and are indicative of hepatic cirrhosis, with some rare exceptions. The serum albumin and globulin levels are also consistent with liver disease, as is the elevated urinary excretion of urobilinogen. The presence of ascites was suggested on physical and by x-ray examinations and was confirmed by the abdominal tap. This may, of course, have been due to other intra-abdominal disease rather than to a decompensated liver.

If the patient had liver disease, is it possible to decide upon its type? The gross findings at operation suggested portal cirrhosis rather than a toxic type. The nodular regenerative hyperplasia described in the biopsy report might be associated with either type of cirrhosis. Purely on what the surgeon saw at operation I shall decide in favor of a portal cirrhosis. At this point it would be interesting to know something about this patient's previous alcoholic history.

DR. BENJAMIN CASTLEMAN: She had no history of alcoholic intake.

DR. SHORT: The next point to settle concerns the suggestion in the biopsy of the presence of primary liver-cell carcinoma. Although severe pain is frequently a manifestation of portal cirrhosis, it is more common when cancer has appeared, occurring in over three fourths of the cases in one series. Furthermore, I can best tie in this patient's subsequent intra-abdominal disease by making a diagnosis of hepatoma in addition to the cirrhosis.

I should like to review the events that led to the final admission. First, the abdominal pain became more severe. Then abdominal swelling developed, — I do not know whether it was due to ascites or gaseous distention, — and tarry stools were passed. On the day before admission the patient had severe diarrhea. In the hospital there were three important abdominal findings. The first was the presence of ileus as demonstrated by the gas-filled loops of bowel in the abdominal x-ray film and by the absence of peristalsis. The second was the development of peritonitis, indicated by the increased abdominal tenderness and spasm and by the nature of the ascitic fluid, which was cloudy with a protein value suggestive of an exudate, which contained an increased number of white cells with a high percentage of polymorphonuclear leukocytes and which grew organisms on culture. Finally, there was evidence of intestinal bleeding both in the stool examination and in the material aspirated by the Miller–Abbott tube. To my mind diarrhea followed by ileus, intestinal bleeding and peritonitis adds up to mesenteric thrombosis. Without going into a discussion of other causes of intestinal catastrophes of this nature, I should like to suggest a diagnosis of mesenteric-vein thrombosis in this patient. Thrombosis of the portal system is found occasionally as a terminal event in portal cirrhosis, but much more frequently when primary carcinoma of the liver is present — in perhaps a fourth of the cases.

I still have not explained the mental confusion and drowsiness. Perhaps she was just a very sick woman of sixty-seven in whom no definite cause was found. The liver disease may well have contributed to her mental state. Another possibility is cerebral metastases from a neoplasm if one was present. In the absence of focal signs I do not believe I can be sure of the last.

In summary, I believe this patient's illness can be explained by the following sequence of events: portal cirrhosis of the liver, primary carcinoma of the liver and finally portal thrombosis with a spread into the mesenteric veins.

DR. JACOB LERMAN: We suggested that the drowsiness was due to the opiate she was taking. She took a good deal of it.

DR. SHORT: Also, if she had liver disease, the effect of opiates was probably prolonged.

CLINICAL DIAGNOSES

Mesenteric thrombosis.
Hepatic failure.

DR. SHORT'S DIAGNOSES

Portal cirrhosis of liver.
Primary carcinoma of liver.
Thrombosis of portal and mesenteric veins.

ANATOMICAL DIAGNOSES

Thrombosis of portal and mesenteric veins.
Infarction of small bowel.
Cirrhosis of liver, post-necrotic type.
Ascites.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy there was in the abdominal cavity 3500 cc. of cloudy, slightly hemorrhagic fluid, which was apparently a combination of ascitic fluid and fluid produced by irritation of the peritoneum. The peritoneal irritation was caused by gangrene of the areas of small bowel, which had been produced by mesenteric-vein thrombosis, as Dr. Short suggested. The liver was atrophic, weighing under 900 gm., and was the site of a post-necrotic type of portal cirrhosis. The nodules of regeneration varied in size from 2 mm. up to 3 cm., suggesting that it was not the alcoholic or Laënnec type of cirrhosis but atrophic or so-called post-necrotic cirrhosis.

DR. SHORT: Could these nodules have been seen at operation?

DR. CASTLEMAN: Yes; I think so. We reviewed the slide on which a diagnosis of regenerative hyperplasia or hepatoma had been made and believed that there were only islands of regeneration and no evidence of hepatoma.

The portal vein, for its entire length, and its main intrahepatic branches were almost completely thrombosed; the thrombus was rather old and extended as more recent thrombus into the superior mesenteric and splenic veins. There was some extension into the midcolic vein, but it apparently had not produced any change in the large bowel. The superior mesenteric artery was normal. There were three segments of small bowel that were infarcted, one in the jejunum 45 cm. long and two in the ileum 15 and 20 cm. in length. In places the mesentery also was gangrenous. The spleen was enlarged, as one would expect with portal cirrhosis.

It is interesting to speculate on the sequence of events. Did the patient have, at the time of the first operation, a portal-vein thrombosis? Certainly, the findings at autopsy were consistent with a portal-vein thrombosis that had continued for four or five weeks. I am wondering whether the trauma of the operation initiated the retrograde thrombosis into the superior mesenteric vein from a previously existing portal-vein thrombosis. Of course, that

might occur spontaneously as well. From the history it seems that the events started immediately after the operation, and perhaps the portal-vein thrombosis began at that time.

DR. SHORT: Was the portal vein completely occluded?

DR. CASTLEMAN: It was almost completely occluded; the thrombus extended into the radicles within the liver.

DR. SHORT: A portal-vein thrombosis is a very serious event, even without spread to the mesenteric vessels.

DR. CASTLEMAN: Yes; it would perhaps mean that she did not have the occlusion, at least not all of it, at the time of the first operation. We do know, however, that mesenteric-vein thrombosis producing changes in the bowel may continue for weeks or even months.

CASE 38432

PRESENTATION OF CASE

A thirty-five-year-old woman, gravida IV, para IV, was admitted to the hospital because of intermenstrual bleeding.

The patient had a normal menarche at fourteen years of age and subsequently had four full-term normal pregnancies. The menstrual periods, which had not been abnormal, had occurred every twenty-five days, lasting four days. The last menstrual period had begun at the expected time twenty days before entry to the hospital, but bleeding had persisted. There was no associated pain or other symptoms, and the flow was bright red, requiring one pad per day. Otherwise, the patient felt generally well. There was no history of hormone medication and no symptoms of menopause.

Four years before admission the patient underwent a splenectomy after injuries received in an automobile accident, and two and a half years prior to entry she had an episode diagnosed as infectious mononucleosis unconfirmed by laboratory examination.

Physical examination showed a well developed and well nourished woman in no distress. The heart and lungs were normal. There was a well healed left-upper-quadrant paramedian scar. The abdomen was soft and nontender. No masses were felt, and normal peristaltic sounds could be heard.

The temperature, pulse and respirations were normal. The blood pressure was 95 systolic, 75 diastolic.

Examination of the urine was negative. The blood hemoglobin was 12 gm., and the white-cell count 16,300, predominantly mature neutrophils. The platelets numbered 2,000,000 per cubic millimeter.

In the hospital a pelvic examination and dilatation and curettage were carried out under ether anesthesia. The uterus was in retroversion, somewhat globular, definitely enlarged and freely movable. The cervix was clean, and no masses could be felt in either vault. Routine dilatation and curettage demonstrated a canal 9 cm. in depth, with a posterior distortion that was thought to be due to a leiomyoma in the posterior wall of the uterus. There was a moderate amount of tissue, which subsequent histologic examination showed to consist of decidua and placental villi.

About nine hours later the patient began to have severe, crampy lower abdominal pain aggravated by ambulation and relieved once for a short while by Demerol. She was nauseated and vomited once. Examination at this time was negative. Both symptoms persisted throughout the night.

On the following morning physical examination showed voluntary low abdominal spasm but no masses. On rectal examination the uterus was retroverted, hard and tender and could not be moved. No other masses were found. The patient was given morphine and placed on bed rest. Twenty-four hours later the cramps and the vaginal staining had ceased. One day later, the abdomen was slightly distended but less tender than before. On rectal examination the uterus seemed smaller but was still very tender. The blood hemoglobin was still 12 gm., but the white-cell count was 18,000. A blood smear was interpreted as showing a post-splenectomy and probably postoperative mild thrombocytosis. Because of this and the anticipation that operation would be required, Dicumarol therapy was begun.

Two days later, on the seventh hospital day, the patient appeared somewhat more rested, and the abdomen was soft and nondistended. However, an extremely tender mass was palpable just above the pubis on the left, although the remainder of the tenderness had decreased. Later the same day an operation was performed.

From the third to the seventh hospital day the temperature ranged from 99 to 100°F., and the pulse from 80 to 90. Respirations were normal.

DIFFERENTIAL DIAGNOSIS

DR. MARSHALL K. BARTLETT*: As a point of departure, we can accept the fact that this woman was pregnant and that she had an intrauterine pregnancy as shown by the presence of both decidua and placental villi in the curettings. Whether it was a viable pregnancy or a partial miscarriage I see no way of determining, and I do not think it is of any great importance to the later events. A complication of this pregnancy obviously developed after the dilatation and curettage.

What are the possibilities? We should first think of infection. It is possible that the story about the events prior to admission was not entirely accurate. Perhaps some previous instrumentation had been performed, although there was no evi-

*Visiting surgeon, Massachusetts General Hospital.

dence of that on admission. The first examination certainly showed nothing to suggest a perforation of the uterus with infection. It seems to me unlikely that that would prove to be the problem. Did a perforation occur at the dilatation and curettage, with subsequent sepsis? Apparently, the patient did not have any pain immediately after operation but experienced severe pain suddenly about nine hours later. During that time and on subsequent days she never had any great elevation of temperature. I think that would be an unusual combination of events for sepsis resulting from mechanical perforation of the uterus. The onset would have been more insidious, and the febrile reaction would have been more striking.

The type of pain described sounds as though it were due to bleeding into the pelvic cavity. It is possible that she had an ectopic pregnancy in addition to the intrauterine one. This is a relatively rare condition, but several hundred such cases have been reported in the literature,* so that I must consider the possibility that bleeding from an ectopic pregnancy in one of the tubes was present in addition to the intrauterine pregnancy and that this was the cause of the sudden onset of pain. Another possible source of bleeding in this stage of pregnancy is the corpus luteum. That was an unknown entity to me until two or three years ago, when I saw 2 such cases in rapid succession in the Emergency Ward. Both those patients had fairly massive bleeding from the corpus luteum of pregnancy. They were in the early stages of pregnancy, about six weeks from the last menstrual period, and the picture of ectopic pregnancy developed in both.

Another possibility is interference with the blood supply to some organ in the pelvis. There are several ways in which that could occur. It will be remembered that at the time of dilatation and curettage a posterior distortion of the uterus, thought to be due to a leiomyoma, was noted. If that observation was correct, and if a leiomyoma was present, it is possible that after the dilatation and curettage something occurred that interfered with the blood supply of that fibroid, infarction of which could certainly have caused the sudden onset of fairly severe pain and could explain the later chain of events. An ovarian cyst may have become twisted on its pedicle. There was no note of any mass outside the uterus until the final examination on the seventh hospital day, when the presence of a mass above the symphysis was noted. If she had an ovarian cyst, it escaped detection. Although that does not rule out the presence of a cyst, it makes me a little less willing to accept that diagnosis. Torsion of one of the tubes might explain this picture. Torsion of a normal tube is quite a rare event. Since this woman became pregnant shortly before this episode, I must assume that she had at least one normal tube. If she had a hydrosalpinx, it was not felt. I think that torsion of a tube is a fairly remote possibility.

Is it possible that this condition was due to something not connected with the pelvic organs? An acute diverticulitis of the sigmoid in addition to the pregnancy should be considered. However, it seems to me that the physical findings on the various examinations make it rather unlikely that this was a lesion as remote from the uterus as the sigmoid. Diverticulitis is rare in this age group and is a rare complication of pregnancy, and I shall therefore rule it out.

Of the possibilities that I have mentioned it seems to me that the one that fits in best with the symptoms and physical findings is a fibroid whose blood supply for some reason was impaired after the operation. As a second diagnosis I should choose an ovarian cyst with a twisted pedicle.

A PHYSICIAN: An Aschheim–Zondek test was not done on this patient before any operative procedure was performed?

DR. BARTLETT: It was not reported.

A PHYSICIAN: Would you consider a placenta accreta that had ruptured through the uterine wall?

DR. BARTLETT: I should think that it would be too early in pregnancy for that to occur.

A PHYSICIAN: Would you consider the possibility of a traumatic hematoma between the layers of the broad ligament as the result of a perforation that produced a mass above Poupart's ligament?

DR. BARTLETT: I think that is a good possibility; the hematoma may have developed rather slowly. Perhaps the reason her symptoms did not become apparent for some hours was that she had had anesthesia and medication.

DR. BENJAMIN CASTLEMAN: This patient was operated upon by Dr. Ulfelder. It is interesting that his preoperative diagnosis was the same as Dr. Bartlett's.

DR. HOWARD ULFELDER: The problem in this patient, as Dr. Bartlett so ably pointed out, was to determine what happened nine hours after the curettage. I think I should stress the very acute onset of this pain and the severe pain that persisted continuously thereafter. She was perfectly conscious and rational within less than an hour of the curettage. I saw her and various other people saw her in the interval between the curettage and the onset of the pain; she was out of bed, reading, eating and perfectly comfortable and free from pain. She required no medication after the curettage.

The question of an unrecognized perforation that occurred at the time of curettage was seriously raised. I was not aware that a perforation had occurred. Moreover, as we observed her and as this tender mass became manifest, I decided that the fibroid, which I had already suspected of being present, had in some way become infarcted. There

*Lacey, J. T. Two unusual cases of ectopic gestation. *New Eng. J. Med.* 247:359-361, 1952.

was one additional feature in this case: the high platelet count. The blood abnormality presented us with a "red herring," and it was this possibility of an increased tendency to spontaneous intravascular thrombosis that made me suspect an unusual complication secondary to interference with blood supply to an organ.

Clinical Diagnosis

Infarcted uterine leiomyoma.

Dr. Bartlett's Diagnosis

Infarcted uterine leiomyoma.

Anatomical Diagnosis

?Rupture of cornual pregnancy.

Pathological Discussion

Dr. Ulfelder: Exploration revealed an inflammatory mass involving the left tube and ovary, which was bounded by the sigmoid laterally, by the peritoneum of the pelvis and anteriorly by the posterior leaf of the broad ligament and wall of the uterus. This could be freed up gradually except for the tube and ovary, which seemed to be the central focus of this disturbance and could not be dissected out as normal structures. They were therefore removed as a left salpingo-oöphorectomy. The sigmoid was definitely a part of the wall of this mass and was thickened and edematous but obviously was not the site of a primary lesion. There was no evidence that a perforation of the uterus had taken place; whether this excludes that possibility I would not dare say. Certainly, when the mass was freed up from the back of the broad ligament, there was no sign that perforation had occurred previously. It was my impression that we were dealing with an accident that had occurred to the left tube or ovary or both. I could not tell what the accident had been. There was no free blood in the peritoneal cavity and no evidence that massive hemorrhage had occurred in the course of the development of this complication. I believed that I was dealing with a rupture of a tubal pregnancy that had not bled very much because it had sealed off immediately.

Dr. Castleman: In the numerous sections we made through this mass, we found infection and hemorrhage in the tube and ovary, with most of the reaction on the surface of the tube. After we had cut about 20 blocks a few small islands of trophoblastic tissue were noted on the surface of the tube. In most cases of tubal pregnancy one can find in that number of sections more evidence of a pregnancy in the tube especially if the rupture occurs within that short a period. Although I cannot rule out another pregnancy, I should be in favor of considering one of two other possibilities. The first is that during the dilatation and curettage, the curet produced a small rupture of the uterus and perhaps carried through the rupture a few islands of trophoblastic tissue that were still viable at the time we saw them. The other possibility, and perhaps a better one, is that there was an interstitial cornual pregnancy — at the juncture of the tube and the fundus of the uterus — and that the curet had sufficiently traumatized the pregnancy so that the isthmal portion of the tube ruptured. I do not know how to decide this but I assume that it was one of those two possibilities rather than the extremely rare condition of two pregnancies at the same time.

Dr. Ulfelder: There will always be room for some measure of disagreement of the sequence of events here because one has to assume, if Dr. Castleman's ideas are correct, that this was not just perforation of the uterus or just a tubal pregnancy; one has to assume that something happened to the left tube and ovary, which were not normal structures caught up in an inflammatory mass; they were damaged and destroyed, and one would have to assume that the curet went through the uterus and hurt them in some way. I do not know how the findings in the tube and ovary could be explained on the basis of an interstitial uterine pregnancy, unless there was a ruptured cyst or some other complication associated with it. Assuming it was an ectopic tubal pregnancy that had ruptured and ceased to exist seven days before the exploration, I do not know how much identifiable trophoblastic tissue should be present. Most of the patients are operated on within a few hours of the rupture.

Dr. Bartlett: Was the corpus luteum on that side or the other?

Dr. Castleman: There was no evidence of it on the left.

A Physician: What did the fibroid look like at operation?

Dr. Castleman: There was no fibroid.

Dr. Ulfelder: The distortion of the uterus was due to the pregnancy, and the products of conception in the uterus made the canal seem deflected to one side.

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PENNY WISE?

Economies in government, which so many Americans — a majority, it may be hoped — are more or less sincerely supporting, are not equally pleasing when some of them strike too close to home. In the case of the budgetary retrenchments that Congress has dictated for the medical department of the Veterans Administration, considerable apprehension over their probable results is not inconsistent with an over-all desire for the exercise of intelligent caution in the expenditure of the nation's wealth.

It is not the principle of economy that is the present cause for alarm but the method by which such economy is to be effected, in the sacrificing of quality of service, while the quantity remains apparently the same. Impairment of patient care seems inevitable with the proposed dismissal of 2250 hospital employees, a reduction in funds for medical and dental services on a fee basis, and the arbitrary retirement of many of the medical and surgical consultants who have given the service, up to the present, such an unwonted — or should it now be unwanted? — prestige.

It is with some sadness that the bright prospects of the postwar Veterans Administration will be recalled, with such men as Omar Bradley, Paul Hawley and Paul Magnuson in charge of its policies, with deans' committees selecting its personnel and with the entire medical profession and others eager to demonstrate that even in a democracy adequate medical care can be assured the nation's veterans.

Incalculable extravagances were of course encountered in the building of hospitals and more hospitals, and, as was inevitable, a gradual extension of services took place, putting the Government farther and farther into the practice of medicine. It was hoped, however, that the quality of the service, which perhaps only doctors can completely comprehend, might remain on a high level.

Economy, unfortunately, cannot become retroactive to the point of undoing costly and unnecessary building; it can, as the Council of Chief Consultants to the Veterans Administration medical service recommended, dictate the closing of some of the hospitals rather than their continuation in operation on a short-staff basis; it can do something about the continued construction of any further monuments to waste. Economy can help to fulfill its own objective by ensuring the adequate and efficient operation of those facilities that are really necessary.

It would, indeed, be a paradoxical situation to close certain Veterans Administration hospitals while new ones continued to be built; it is only to be hoped that such paradoxes may eventually impress themselves on the consciousness of the still overcomplacent taxpayers.

ACADEMY OF GENERAL PRACTICE

The American Academy of General Practice was established five years ago — at a time when this type of medical care was considered by some to be in its twilight — for the following reasons:

to promote and maintain high standards of general practice of medicine and surgery; to encourage and assist young physicians in preparing, qualifying and establishing themselves in general practice; to protect the right of the general practitioner to engage in medical and surgical procedures for which he is qualified by training and experience; to assist in providing postgraduate study for general practitioners and to encourage and assist physicians and surgeons to participate in this training; and to advance medical science and private and public health.

There is no question that general practice, even without the aid of the Academy, would eventually have regained all the respect and prestige and standing in the profession and with the public that may apparently have been lost in recent years, for general practice is the very hub on which the care of the sick revolves. On the other hand, there is also no question that the Academy provided a rallying ground for general practitioners at a time when they were being shouldered too roughly by their somewhat sophisticated and certainly better organized colleagues in the burgeoning specialties.

With its own amazingly successful organization, general practice has quickly resumed its rightful place as the forward platoon of the medical company. It is an organization on which this unspecialized specialty is to be particularly congratulated, for it is truly academic and relatively nonpolitical, basing the service that it so clearly renders on the qualifications for membership that it requires.

The recent fourth annual clinical meeting of the Massachusetts Academy, under the able leadership of Dr. Harvey A. Kelly, is an example of the progressive spirit of the organization, for half the session was held at the Children's Medical Center, with the Center and the Boston Lying-in Hospital co-operating in the program, the other half being given over to a symposium on arthritis with the participation of various authorities in that field. The Academy, moreover, has joined hands with the New England Postgraduate Assembly and the newly organized Postgraduate Medical Institute to offer to its members the best in modern postgraduate instruction.

Apparently, the stone that refused to be rejected has remained as the cornerstone of the temple — to pile metaphor upon metaphor.

THE GLORIOUS FOURTH

On July 4, 1952, the bill (S2337) to establish a program of maternity and infant care for servicemen's wives and infants was favorably reported to the Senate by Herbert H. Lehman for the Committee on Labor and Public Welfare. On the same day — which only by coincidence happened to be Independence Day — arguments on behalf of the bill were again presented in a news release to the public. Nothing new was contained in this repetition of arguments beyond those previously disseminated and commented on editorially in the *Journal*.

Senator Lehman's main argument remained the same — that it is essential to morale to assure the man serving in the armed forces that his pregnant wife and his pre-school children will be able to get the medical care that they need. The validity of this principle has been freely admitted so that the real bone of contention has been whether the Government should go back into the practice of obstetrics and pediatrics as it did during the last war in the EMIC program in order, as Senator Lehman phrased it, to create the "machinery to deal with the much larger problem which might arise overnight if the world crisis should suddenly worsen." This too is a cogent argument, although, unlike the basic principle of making medical care of high quality available to servicemen, it is subject to vigorous debate, for here is the foot in the door to socialized medicine, with the toes of that foot encased in the shoe of "emergency" legislation.

On the last page and in the closing three paragraphs of the news release is a terse acknowledgment that "at hearings on this legislation the American Hospital Association and the Blue Cross Commission proposed an alternative plan for medical and hospital insurance for dependents of servicemen, based on voluntary deductions for servicemen's pay to cover premiums, with the possibility of a Federal contribution to cover part of such premiums."

The news release from the Subcommittee on Health of the Senate Committee on Labor and Public Welfare closes with a bland brush-off: "A special hearing to explore the American Hospital Association — Blue Cross Proposal made it clear

that it is not practical nor possible through voluntary health insurance systems alone to assure adequate and uniform coverage and protection for the prenatal delivery and postnatal care of the serviceman's wife or for the care of his baby and pre-school children." No arguments, no reasons, no analyses are given for rejection, — simply, "a special hearing . . . made it clear," — so clear that the item can be tucked, single-spaced in the interest of thrift, into the tail end of a bulletin released for publication on the glorious Fourth.

THE RED FEATHER CAMPAIGN

THIS year the United Community Services, whose Red Feather Campaign begins on November 10 and closes on December 4, has announced a goal of $7,283,000. The figure is $857,000 more than the amount raised last year, the increase being due mainly to the inflation that, in spite of more than a decade of "controls" of various sorts, has plagued the economy and drastically reduced the purchasing power of the American dollar. Other explanations for the higher goal are the growing social problems caused by juvenile delinquency, care of the aged, disruption of families and off-duty needs of youthful servicemen.

In addition to the support given to the 300 member agencies in Greater Boston, the goal of the Red Feather Campaign includes $512,992, which is the Boston quota of the national total of $19,451,340 to be raised to finance the six activities of the United Defense Fund: USO, American Social Hygiene Association, American Relief for Korea, United Community Defense Services, National Rehabilitation Association and National Seamen's Service. The funds raised during the campaign now go for the help, in one way or another, of 1 out of every 3 workers in the community or members of their families.

As in previous years, one contribution means support given to a multitude of charities. An effort has been made to avoid the deluge of separate appeals that, at one time, made the fall of the year a nightmare for the busy professional man — the multiple solicitations from agents in residential and office areas, as well as from hospitals and even medical schools. This year the central committee of the campaign, through the President of the Massachusetts Medical Society, has urged doctors to indicate on a return post card the place where they prefer to make their contributions: at a hospital or medical school or in the office. It must be realized that this excellent plan will probably not at first be completely successful. Patience on the part of the physician who happens to be approached more than once will, it is hoped, eventually be rewarded by elimination of the annoyance.

The Red Feather Campaign has become a symbol of the American way of helping the unfortunate members of the community. Voluntary contributions by the citizenry finance the worthy objectives of building health, caring for children, keeping families together, providing recreation and guidance for youth, rehabilitating the handicapped and promoting friendly relations among people of all races and creeds. The appeal on behalf of these activities deserves the utmost support of every member of the community.

A horse actually dropped down dead, from fright at seeing a locomotive and train coming in at Frankfort, Ky.

Boston M. and S. J., *Oct. 27, 1852*

OBITUARY

ARTHUR KINGSBURY STONE

1861–1952

A native of Boston, Arthur K. Stone was educated at Framingham High School and Academy and at Harvard College, from which he graduated in 1883. Five years later he received his medical degree from Harvard Medical School.

His name was long associated with the fight against tuberculosis, on both the local and the national level. He was chairman of a board of trustees appointed by the Governor to supervise the care of tuberculous patients in Massachusetts. He was a director of the National Tuberculosis Association and became one of its first authorities on the disease, witnessing and participating in the efforts at control that eventually caused tuberculosis to drop from first to fifth place (exclusive of accidents) among the leading causes of death in the United States.

Dr. Stone's activities included work at the House of the Good Samaritan, where he was at one time chief of staff, and great interest in the affairs of the Massachusetts Medical Society, of which he was a councilor for many years and treasurer from 1917

to 1931. In addition, he was secretary-treasurer of the American Clinical and Climatological Association. In 1915 the Governor appointed him to a committee of directors to reorganize the Massachusetts Department of Public Health.

Arthur Kingsbury Stone will be remembered as the kind and genial friend, as well as the active and devoted physician and man of science. His long and productive life closed on July 31, when he died in his ninety-first year.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CAINES — Richard J. R. Caines, M.D., of Bay Pines, Florida, formerly of Petersham, died on August 11. He was in his seventy-seventh year.

Dr. Caines received his degree from Tufts College Medical School in 1914.

He is survived by his widow and two sons.

ELY — Richard S. Ely, of West Townsend, died on October 8. He was in his eighty-seventh year.

Dr. Ely received his degree from Dartmouth Medical School in 1891. He was a former president of Worcester North District Medical Society and a former member of the Board of Health and was a fellow of the American Medical Association.

He is survived by his widow.

HALLORAN — Edward J. Halloran, M.D., of Worcester, died on September 11. He was in his sixty-first year.

Dr. Halloran received his degree from Jefferson Medical College of Philadelphia in 1921. He was formerly cardiologist at Memorial Hospital and physician to the Worcester Office of the Veterans Administration. He was a fellow of the American Medical Association.

He is survived by several cousins.

HUYCK — Clifford J. Huyck, M.D., of West Brookfield, died on August 31. He was in his eightieth year.

Dr. Huyck received his degree from Cleveland University of Medicine and Surgery in 1896. He was a member of the staff of Westboro State Hospital, and was a member of the Association of Military Surgeons of the United States and a fellow of the American Medical Association.

He is survived by his widow and two daughters.

JURIST — Charles Jurist, M.D., of Springfield, died on September 1. He was in his sixty-first year.

Dr. Jurist received his degree from New York University College of Medicine in 1914. He was chief of the pediatric section of Springfield Hospital and was a member of the New England Pediatric Society and a fellow of the American Medical Association.

He is survived by his widow, two daughters, five grandchildren, his father, two brothers and a sister.

MARVELL — Mary W. Marvell, M.D., of Fall River, died on August 11. She was in her eighty-second year.

Dr. Marvell received her degree from Johns Hopkins University School of Medicine in 1900. She was formerly a member of the staff of Union Hospital and a member of the Board of Public Welfare, as well as a physician on the staff of the Wellesley College Rehabilitation Unit.

She is survived by a brother, three nephews and a niece.

MCCARTHY — Lawrence D. McCarthy, M.D., of Chelsea, died on September 18. He was in his fifty-second year.

Dr. McCarthy received his degree from Tufts College Medical School in 1928. He was a former president of Suffolk District Medical Society and was a member of the staff of Chelsea Memorial Hospital. He was a member of the National Gastroenterological Association and a fellow of the American College of Surgeons and American Medical Association.

He is survived by his widow, a son and his father.

PERRY — Edward L. Perry, M.D., of Middleboro, died on September 23. He was in his fifty-third year.

Dr. Perry received his degree from Boston University School of Medicine in 1922. He was assistant professor of clinical ophthalmology at Boston University School of Medicine, chief of staff at St. Luke's Hospital, and surgeon and former chief of the Outpatient Department of the Eye Clinic, Massachusetts Memorial Hospitals, and was a fellow of the American College of Surgeons and American Medical Association.

He is survived by his widow and a son.

WATERS — James E. Waters, M.D., of Gardner, died recently. He was in his seventy-first year.

Dr. Waters received his degree from Baltimore Medical College in 1905. He was a member of the Massachusetts Society of Medical Examiners.

He is survived by his widow, a son and a daughter.

BOSTON MEDICAL LIBRARY

THE FOUNDATIONS OF BIOGRAPHY

The contributions to medical progress of the eminent French chemist and physicist, Louis Pasteur (1822–1895), are too well known to require particular attention in these papers. His researches included work on crystallography, leading to his discovery of isometric substances; fermentation in relation to wine and beer; and silkworm disease, in which he isolated two distinct diseases of bacillary origin and found a method of preventing contagion as well as one for detecting diseased stock, thus saving the silk industry of France. His attention was next turned to anthrax and to chicken cholera, and he perfected methods of preventive inoculation for both diseases.

His work on hydrophobia in man and on rabies in dogs is well known. After prolonged experiments, he perfected an antirabic preventive vaccine, and on July 6, 1885, had the courage to inoculate with it a child who had been bitten by an infected dog. The result was so successful that in November of the same year, the famous Pasteur Institute was established in Paris.

The life of Pasteur has been written by his son-in-law, René Vallery–Radot and translated into English, and his works in seven volumes, edited by his grandson, Pasteur Vallery–Radot, were published in Paris from 1922 to 1939. The same editor has collected his correspondence, and published the letters in four volumes.[1] They are divided into three parts: 1840–1857 (letters of his youth and on

crystallography); 1857–1877 (fermentation, spontaneous generation, diseases of wine, silkworms, and beer); and 1877–1885 and 1885–1895, in two volumes, covering the period of virulent diseases — chicken cholera, anthrax, hydrophobia and other infections.

Collections of letters of eminent persons form the foundations of biography. In this connection there may be mentioned the letters[2, 3] of Giovanni Battista Morgagni, written to Giovanni Bianchi, 1720–1770, and to Francesco M. Zanotti, 1712–1769.

Morgagni, 1682–1771, was a pupil of Valsalva, and later a professor at Padua, 1715–1771. He was the founder of modern pathological anatomy, bringing into correlation the records of post-mortem findings and clinical records on a grand scale. He gave many descriptions of new forms of disease, including the first recorded case of heart block (Adams–Stokes disease), and first described cerebral gumma and diseases of the cardiac valves. He made pathology a genuine branch of modern medicine.

References

1. Pasteur, L. *Correspondence réunie et annotée par Pasteur Vallery-Radot.* 4 vol. 2118 pp. Paris: Flammorion, 1951.
2. *Carteggio tra Giambattista Morgagni e Francesco M. Zanotti.* 620 pp. Bologna: Nicola Zanichelli, 1881.
3. *Carteggio inedito di G. B. Morgagni con Giovanni Bianchi (Janus Plancus), con introduzione e note del Prof. Guglielmo Bilancioni e un discorso del Prof. A. Bignan.* 290 pp. Bari: Società tipografia editrice Barese, 1914.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST, 1952

Résumé

Disease	August 1952	August 1951	Seven-year Median
Chancroid	0	0	1
Chicken pox	100	200	179
Diphtheria	0	7	17
Dog bite	1196	1322	1184
Dysentery, bacillary	5	2	7
German measles	151	268	47
Gonorrhea	179	175	308
Granuloma inguinale	0	0	0
Lymphogranuloma venereum	0	1	1
Malaria	25	0	1
Measles	103	440	317
Meningitis, meningococcal	4	2	4
Meningitis, Pfeiffer bacillus	4	4	2
Meningitis, pneumococcal	0	1	0
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	1	1	0
Meningitis, undetermined	2	2	4
Mumps	153	386	275
Poliomyelitis	196	94	94
Salmonellosis	11	5	19
Scarlet fever	40	33	72
Syphilis	156	189	187
Tuberculosis, pulmonary	168	186	215
Tuberculosis, other forms	10	17	13
Typhoid fever	4	2	4
Undulant fever	1	0	2
Whooping cough	108	149	475

Comment

Diseases below the seven-year median were chicken pox, diphtheria, measles, mumps, scarlet fever and whooping cough.

No cases of diphtheria were reported for August, which is the second month in succession that this record-breaking event has occurred.

Only twice in thirty-seven years have fewer cases of measles been reported in August.

The 153 cases of mumps made this the lowest figure for any month since September, 1947.

The 40 cases of scarlet fever represented the second lowest figure for any month since 1906. The low record was 33 cases in August, 1951.

Diseases above the seven-year median were German measles and poliomyelitis.

The 196 cases of poliomyelitis, although above the seven-year median, represented a figure considerably lower than the 719 cases reported for August, 1949.

Geographical Distribution of Certain Diseases

Dysentery, bacillary, was reported from: Beverly, 1; Milton, 1; Danvers, 3; total, 5.

Encephalitis, infectious, was reported from: Belmont, 1; Newburyport, 1; Springfield, 1; total, 3.

Hepatitis, infectious, was reported from: Camp Edwards, 1; Leicester, 1; Newton, 1; Otis Air Force Base, 1; Worcester, 6; Wrentham, 28; total, 38.

Lymphocytic choriomeningitis was reported from: Holden, 1; Leominster, 1; Worcester, 1; total, 3.

Malaria was reported from: Camp Edwards, 10; Everett, 1; Fort Devens, 13; Springfield, 1; total, 25.

Meningitis, meningococcal was reported from: Danvers, 1; Holyoke, 1; New Bedford, 1; Stoneham, 1; total, 4.

Meningitis, Pfeiffer bacillus, was reported from: Malden, 1; Quincy, 1; Waltham, 1; Worcester, 1; total, 4.

Meningitis, streptococcal, was reported from: Cambridge, 1.

Meningitis, undetermined, was reported from: Haverhill, 1; Worcester, 1; total, 2.

Poliomyelitis was reported from: Amesbury, 1; Ashland, 2; Attleboro, 1; Beverly, 4; Boston, 19; Brookline, 3; Burlington, 1; Cambridge, 2; Canton, 1; Chatham, 1; Chelsea, 5; Chicopee, 1; Cohasset, 1; Danvers, 1; Dartmouth, 1; Everett, 4; Fall River, 1; Falmouth, 1; Framingham, 2; Grafton, 1; Greenfield, 2; Groveland, 1; Harvard, 1; Haverhill, 2; Holyoke, 2; Hopedale, 1; Hopkinton, 1; Hudson, 1; Lawrence, 1; Leominster, 1; Lexington, 1; Lowell, 5; Lynn, 18; Lynnfield, 1; Malden, 5; Mansfield, 1; Marblehead, 1; Marshfield, 1; Medford, 8; Melrose, 2; Merrimac, 1; Methuen, 1; Milford, 1; Natick, 2; Needham, 2; Newburyport, 2; Newton, 6; North Andover, 1; Norwood, 3; Oxford, 1; Palmer, 1; Peabody, 2; Pittsfield, 2; Plymouth, 2; Quincy, 1; Reading, 1; Revere, 7; Salem, 6; Salisbury, 1; Saugus, 1; Scituate, 1; Sharon, 1; Sherborn, 1; Somerville, 4; Springfield, 3; Stockbridge, 1; Stoneham, 3; Swampscott, 2; Walpole, 1; Waltham, 2; Watertown, 2; Wellesley, 5; Westfield, 7; West Springfield, 4; Wilmington, 1; Worcester, 5; total, 196.

Salmonellosis was reported from: Boston, 3; Leominster, 1; Melrose, 1; Quincy, 1; Saugus, 2; Woburn, 1; Worcester, 2; total, 11.

Septic sore throat was reported from Boston, 1; Quincy, 1; total, 2.

Tetanus was reported from: Chelmsford, 1; Melrose, 1; total, 2.

Trichinosis was reported from: Cambridge, 2; Dedham, 1; total, 3.

Typhoid fever was reported from: Holyoke, 1; Plymouth, 1; Weymouth, 1; Worcester, 1; total, 4.

Undulant fever was reported from: Chelsea, 1.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The November schedule of the Consultation Clinics for Crippled Children in Massachusetts is as follows:

Orthopedic Clinic	Date	Clinic Consultant
Salem	November 3	Paul W. Hugenberger, M.D.
Gardner	November 4	Carter R. Rowe, M.D.
Haverhill	November 5	William T. Green, M.D.
Greenfield	November 6	Charles L. Sturdevant, M.D.
Lowell	November 7	Albert H. Brewster, M.D.
Lynn*	November 10	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Brockton	November 13	George W. Van Gorder, M.D.
Pittsfield	November 19	Edward J. Coughlin, Jr., M.D.
Hyannis	November 20	Paul L. Norton, M.D.
Worcester	November 21	John W. O'Meara, M.D.
Fall River	November 24	David S. Grice, M.D.
Springfield	November 26	Garry deN. Hough, Jr., M.D.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

Rheumatic-Fever Clinic	Dates
Fitchburg	November 5, 12, 19, 26
North Reading	November 4, 18, 25

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

TRAINING OF NEGRO GIRLS AS NURSES

To the Editor: In the September 18 issue of the *Journal*, a letter from Dr. William Worthy states that "early in 1929 no Boston Hospital would admit Negro girls to train for nurses." I should like to correct Dr. Worthy.

In 1879 Mary Mahoney graduated from the New England Hospital for Women and Children School of Nursing as the first trained Negro nurse in America. Since that time the New England Hospital for Women and Children admitted qualified young Negro women to the School of Nursing until the school was suspended in 1950.

I do not know where Dr. Worthy received his information, but our records here prove these statements. The New England Hospital for Women and Children not only graduated America's first trained nurse, Miss Linda Richards, in 1873, but also has the distinction of graduating the first trained Negro nurse, Miss Mary Mahoney in 1879.

Dorothy M. Douglas
Director, Nursing Service
New England Hospital
Boston, Massachusetts

REVOCATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held September 10, 1952, the registration of Dr. Pierre Victor Brunelle, of Lowell, was revoked.

Robert C. Cochrane, M.D.
Secretary
State House, Boston

SUSPENSION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held September 10, 1952, the registration of Dr. Kenneth T. Moore, of Hanover, was suspended because of ill health.

Robert C. Cochrane, M.D.
Secretary
State House, Boston

EMPHYSEMA AND MYOCARDIAL INFARCTION

To the Editor: I was much interested in the article entitled "Spontaneous Mediastinal Emphysema and Acute Myocardial Infarction" in the August 28 issue of the *Journal* because I had a similar experience in my practice. This fifty-six-year-old man was hospitalized in June, 1950, with an anterior myocardial infarction. There was inversion of the T waves in Leads 1, AVL, V_3, V_4, V_5 and V_6 and of the Q waves in Leads V_4, V_5 and V_6. He was treated in a routine manner and discharged in about three weeks on a maintenance dose of digitalis.

He was admitted in November, 1951, with a similar episode. When seen he was in shock with a blood pressure of 90 systolic, 60 diastolic, and rapid, thready pulse. He was started on oxygen by nasal catheter. He went into congestive heart failure and was treated with aminophylline and mercurial diuretics. On the sixth hospital day a subcutaneous emphysema of the entire upper anterior part of the chest, neck and face developed, and his eyes were swollen shut. This was rapidly progressive. While preparations were being made to incise the skin and aspirate the air, the nasal catheter was switched from one side to the other, and in a period of forty-five minutes the subcutaneous emphysema had practically disappeared.

I thought that there was perhaps a small ulceration in the mucosa at the tip of the nasal catheter and that oxygen was being blown into the subcutaneous space. I did not think at the time of the necessity of analyzing the subcutaneous gas, but this would have given a good indication of whether the nasal catheter was responsible. I note the patient in Case 1 of the report as pictured receiving oxygen intranasally, and I wonder if these cases cannot be explained on the same basis. My patient, who recovered after a stormy course, had no more difficulty with subcutaneous emphysema.

W. M. Burget, M.D.
Astoria, Oregon

WITH JUSTICE TO ALL

To the Editor: The lead editorial, "Proposed New Medical School in Massachusetts," in the June 12 issue of the *Journal* states the purpose of the new school in Boston recommended by Governor Dever's commission to be "to increase the number of physicians practicing in the State and thus to relieve an alleged shortage." In the *Journal* of September 18 the editorial "The Refugee Physician" comments on the paper by Dr. Alex. M. Burgess and the absurd licensing requirements the Commonwealth of Massachusetts has imposed on foreign physicians.

It is commendable that Governor Dever and his commission believe that the people of Massachusetts need more physicians. It is deplorable to sacrifice this need to the political establishment of a new medical school when properly qualified refugee physicians could step in immediately.

I am no ethereal idealist; it is obvious that the assimilation of foreign physicians entails difficulties. Nevertheless, the minimal standards of fairness, the bonds of fellowship we are told exist among members of the profession and the universal desire to improve medical care should not play second fiddle to political expediency.

Hugh P. Hermann
Third-Year Student, Harvard Medical School
Boston, Massachusetts

LIMITATIONS OF LUMBAR SYMPATHECTOMY

To the Editor: It is becoming increasingly apparent that lumbar sympathectomy fails to do much for postphlebitic disease or varicose stasis, except in rare cases, in which associated arterial disease is present. In spite of this, lumbar sympathectomy seems to have become a standard procedure in stasis, ulceration, edema and dermatitis.

I believe that this approach, which was based on good theoretical grounds, has been given an adequate trial and should no longer be considered except in the rare circumstances mentioned.

Edward A. Edwards, M.D.
Boston, Massachusetts

REGARDING MIKE HAMMER

To the Editor: Your thought-provoking editorial "Sherlock Holmes vs. Mike Hammer" prompts me to attempt an explanation of the wave of sadism that is pervading American literature.

Most psychiatrists will agree that the normal human mind — if there is such a thing as normalcy — contains elements of sadism as well as masochism and that these aberrations in their marked form are actually not completely alien but represent maldevelopment of pre-existing tendencies. Repression of hostility and of sexual urges — increasingly demanded in this overpopulated and overly smooth civilization — makes for increased buildup of perverted urges and cravings.

Sublimation, instead of repression, being the normal outlet for socially unacceptable instincts, creative activity of body and mind is the known preventive factor to forestall aberrations.

I believe that in the last fifty years there has been a catastrophic decline of creative individual activity in this country. Many people have shifted from active, health-sustaining pleasures, like hiking, playing sports, making music and talking to friends, to the passive ones "taking in" the show,

listening to the famous band and watching the game. What remained of the art of conversation and debate was ruined by television, which substituted the efforts of accomplished talkers and entertainers.

I believe that the personality structure of the man of this century is being impoverished and that important safety valves are being closed by this shift from give-and-take to taking in, listening and watching — merely passive pleasures that permit dangerous and devious impulses, occurring in all men, no safe and sane escape.

GEORGE VASH, M.D.

Chicopee, Massachusetts

GREAT OAKS FROM LITTLE ACORNS GROW

To the Editor: In the *Journal of the American Medical Association* (*149*:907-912, 1952) there is an interesting article by William P. Murphy entitled "Twenty-five Years' Experience in Treatment and Management of Pernicious Anemia." Dr. Murphy refers to the early (1849 and 1855) reports by Thomas Addison, Barclay, Fenwick and Anton Biermer. G. H. Whipple's work (May, 1925) is mentioned, as are those of W. Hunter (1888), H. Eichhorst (1878) and E. J. Cohn (1928, 1930), in addition to M. Gaüsslen's (November 8, 1930) injectable liver extract, and Achard and Hamburger's parenteral liver therapy (September 20, 1930).

The monograph by A. Hay Smith, of Bradford, England (*Acute Aplastic Anemia — Its Relation to a Liver Hormone*, London, 1928), in which he reported the use of liver injections in aplastic anemia, and the publications of early reports on the value of liver therapy by Professor Maurice Perrin (Nancy) in 1904, 1905 and 1908, Paul Carnot (1898–1910) and his co-workers in France, and Professors Pietro Francesco Castellino and Alfonso Pirera, of the University of Naples, and others, deserve mention in a review on liver therapy.

Of interest in connection with Dr. Murphy's review are the following articles: *New England Journal of Medicine*, **211**: 986-987, 1934; *Medical Life*, New York, April, 1937; *Journal American Medical Association* **138**:873, 1948 by Hyman I. Goldstein; the articles by J. Mouras (1901) and Maurice Perrin; and the paper by A. L. Skoog entitled "Liver Therapy Advocated During the Last Century for the Anemias" (*Bulletin Hist. Med.* **19**:233–235, 1946).

Observations on the value of liver therapy were made during the early years of this century and appeared in French, Italian and German literature. C. S. Engel (Berlin: 1898) used "Sanguiniform," made of fetal liver, stomach and spleen, and noted the erythrocytic and granulocytic response to such therapy. J. Mouras, Maurice Perrin, Spillman, Gilbert, Carnot, Vidal and other Frenchmen noted the improvement in the blood of patients suffering from cirrhosis of the liver (and macrocytic anemia?) during the period 1898–1910. Walter Channing, in 1842, and James S. Combe, in 1821 and 1822, observed and described "progressive pernicious anemia" as an "idiopathic anemia." Combe's patient definitely had a type of pernicious anemia. Blood counts, of course, were not done, and so Channing, Combe, Addison and the others presented no hemograms. K. Nierordt (1852) and H. Welcker (1854) first reported on blood counts, although in 1746, V. Menghini had discovered iron in the blood. To George R. Minot, William P. Murphy, George H. Whipple and William B. Castle, of course, must be given full credit for monumental and epochal contributions, which definitely led to the universal use of liver therapy, but one must not forget the earlier works in this field of investigation. "But these are deeds which should not pass away, and names that must not wither" (Byron).

HYMAN I. GOLDSTEIN, M.D.

Camden, 4, New Jersey

Note: As a fitting climax to Dr. Goldstein's recital, Hume's story (*Doctors East, Doctors West*. 278 pp. New York: W. W. Norton and Company, Incorporated, 1946) of the Chinese physician of the old school, in Amoy, might be mentioned. This practitioner of half a century ago cured a patient with pernicious anemia with large doses of crow's liver, after her Occidental physician had given her up. — Ed.

NONCLINICAL NOTES

NEW ADMINISTRATOR

The Board of Directors of the New England Hospital announces the appointment of Miss E. Vera Dean, R.N., as administrator.

Miss Dean, who had been active in public-health work for fifteen years before entering the hospital field, was administrator of the W. B. Plunkett Memorial Hospital, Adams, Massachusetts, from 1944 until 1951.

BOOK REVIEW

A Bio-Bibliography of Edward Jenner, 1749-1823. By W. R. LeFanu. 8°, cloth, 176 pp., with 29 plates and frontispiece. Philadelphia: J. B. Lippincott Company, 1951. $16.00. (Limited numbered edition.)

Mr. LeFanu has done for Edward Jenner what Miss Janet Doe did for Andreas Vesalius: provided a living bibliography of one of the great benefactors of mankind. Jenner discovered vaccination for smallpox and brought under control the dread disease that had ravaged the world throughout the ages. His first publication, *An inquiry into the causes and effects of variolae vaccinae* (London, 1798), was followed by *Further observations on the variolae vaccinae, or cow pox* (London, 1799). Both were published in a number of editions in English and translated into foreign languages. Jenner, in his early life, prior to the smallpox work, was interested in zoölogic questions and wrote a number of papers on animals. Naturally, he was also medically inclined and communicated a number of papers to the Fleece Society, a gathering of physicians, instituted in 1788. He was particularly interested in diseases of the heart; his observations on angina pectoris are notable. He was poetically inclined and produced a large large number of poems. He was prolific in his writing, and LeFanu has gathered together all his known writings, in manuscript and in the printed form. Likewise, all known letters are listed in chronologic order, from 1773 to 1823. The text concludes with a chapter on biographies, dedications and portraits. There is also a chronologic table of events in the life of Jenner from his birth on May 17, 1749, to his death on January 26, 1823, and on to his last recorded publication in 1949. There is an index of recorded copies showing the holdings of libraries in Great Britain, Australia, Europe, Canada and the United States. The publishing is excellent, the facsimiles of title pages being especially good. The book should be in all medical and public libraries.

JAMES F. BALLARD

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Das Phaeochromozytom. By Prof. Dr. Heinrich Sack, physician-in-chief, Inneren Klinik der Städtischen Krankenanstalten Krefeld. 8°, paper, 93 pp., with 26 illustrations. Stuttgart: Georg Thieme, 1951. Kartoniert DM 11.70. Distributed by Grune and Stratton, New York.

This small monograph deals with a type of sympathetic-nerve tumor, the pheochromocytoma, or paraganglioma. The subject is discussed thoroughly, including diagnosis, symptomatology, pathological anatomy and pathogenesis. A statistical table concludes the text, and there is a comprehensive bibliography.

Case Record from A Sonnetorium. Cartoons by Edward St. J. Gorey. Illustrated with poems by Merrill Moore. Consultants: Louis Untermeyer, Esquire, Professor John C. Ransom, Henry W. Wells, Ph.D., and William C. Williams, M.D. 8°, cloth, 57 pp. New York: Twayne Publishers, 1951. $1.50.

The "Sonnetorium" here mentioned is a cinder-block laboratory adjacent to the home of Dr. Moore, where are

housed more than one hundred thousand sonnets, written and worked on during his sonnet career. The delightful cartoons by Mr. Gorey depict the trials and tribulations of the sonnet and are supplemented by the verses in sonnet form by Dr. Moore.

The Prevention of Rheumatic Fever. By Lowell A. Rantz, M.D., associate professor of medicine, Stanford University School of Medicine. 8°, cloth, 66 pp. Springfield, Illinois: Charles C Thomas, 1952. $2.25. (Publication No. 125, *American Lecture Series.*)

Dr. Rantz presents the evidence implicating the hemolytic streptococcus as the etiologic agent and discusses the prevention of rheumatic fever. The literature is reviewed, and a bibliography of eighty-three references is appended to the text.

The Skull and Brain Roentgenologically Considered. By C. Wadsworth Schwartz, Ph.B., M.D., associate professor of clinical radiology, College of Physicians and Surgeons, Columbia University, associate clinical professor of radiology, College of Medicine, New York University, consultant to Presbyterian Hospital of New York, Hospital for Special Surgery of New York, and New York City Hospital (Neurological Division), associate attending radiologist, University Hospital, New York City, and Mt. Vernon Hospital, Mt. Vernon, New York, and attending radiologist, St. Agnes Hospital, White Plains, New York; and Lois C. Collins, M.D., associate professor of radiology, College of Physicians and Surgeons, Columbia University, assistant radiologist, Presbyterian Hospital, New York City, associate radiologist, New York Psychiatric Institute, and consultant, United States Marine Hospital, Staten Island, New York. 8°, cloth, 386 pp., with 335 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $10.50.

This valuable semi-atlas has been compiled for the use of persons who may be called upon to examine roentgenograms of the skull and brain. The normal skull is first considered, followed by congenital anomalies, traumatic disorders, tumors, infectious disease and miscellaneous diseases of the skull, brain and its blood vessels. Lists of references are appended to the various chapters, and there is a good index. The book is profusely illustrated with reproductions of roentgenograms, and the publishing is excellent. The volume should be in all neurologic and roentgenologic collections.

A Study of Antimetabolites. By D. W. Woolley, member, The Rockefeller Institute for Medical Research. 8°, cloth, 269 pp. New York: John Wiley and Sons, Incorporated, 1952. $5.00.

This monograph is based on the author's study and investigation of antimetabolites during the past ten years. He discusses their discovery and development, the antagonism between metabolically important compounds and substances related to them in chemical structure and some general aspects of the phenomenon, the mechanism of action of metabolites, their natural occurrence as participants in physiologic processes and as etiologic agents in disease, and their applications to chemotherapy, pharmacology and biochemistry. The concluding chapters deal with designing, synthesis and testing. The pertinent literature is surveyed, and there is a bibliography of 500 items. There are indexes of structural formulas and subjects. The book should be in collections on biochemistry and chemotherapy.

NOTICES

ANNOUNCEMENT

Dr. Joseph W. Copel announces the opening of an office at 372 Marlboro Street, Boston, for the practice of orthopedic surgery.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held at the Beth Israel Hospital on Wednesday, November 5, at 8:15 p.m. A symposium on infection, with Dr. Chester S. Keefer as chairman, will be presented, the following topics being included in the discussion:

Chemotherapeutically Induced Infections. Dr. Louis Weinstein.

Steroid Hormones, ACTH and Cortisone in Infections. Dr. Edward Kass.

Erythromycin (Ilotycin). Dr. Maxwell Finland.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The fall dinner meeting of the Massachusetts Society of Examining Physicians will be held at the Harvard Club of Boston on Wednesday evening, November 5.

After the dinner, Dr. Walter Bauer, Jackson Professor of Clinical Medicine, Harvard Medical School, and chief of the Medical Services at the Massachusetts General Hospital, will speak on the subject "Basis of Diagnosis of Arthritic Changes."

Dr. Russell F. Sullivan, professor of orthopedic surgery, Tufts College Medical School, and chief of the Orthopedic Service, Boston City Hospital, will present the views of the orthopedic surgeon on the relation of trauma to hypertrophic changes, and the Honorable Frank J. Donahue, Justice of the Massachusetts Superior Court, will present his opinion as a jurist on this subject.

All physicians interested in this subject are cordially invited to attend.

HARVARD SCHOOL OF PUBLIC HEALTH SYMPOSIUM ON NUTRITION

The afternoon session of The Symposium on Nutrition presented by the Department of Nutrition, Harvard School of Public Health, will be held on Wednesday, October 29, in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston (off Longwood Avenue near the Children's Hospital). Dr. Charles G. King is chairman.

PROGRAM

2:15 Lipogenesis. Dr. Samuel Gurin, of Philadelphia. Discussion by Drs. Robert P. Geyer and Manfred L. Karnovsky, of Boston.

2:55 Nutrition in Liver Disease. Dr. Paul György, of Philadelphia. Discussion by Drs. Charles Davidson and Kendall Emerson, of Boston.

3:25 Recess.

3:35 The Physiology of Appetite. Dr. John R. Brobeck, of Philadelphia. Discussion by Drs. J. Mayer and Seymour Gray, of Boston.

4:05 Obesity and Body Types. Dr. Edward E. Hunt, of Boston.

4:30 The Measurement of Obesity and the Composition of the Body. Dr. Ancel Keys, of Minneapolis.

NEW ENGLAND HOSPITAL

The monthly clinical conference and meeting of the staff of the New England Hospital will be held in the nurses' home on Thursday, November 6, at 7:15 p.m. Dr. Norman Zamcheck will speak on the subject "The Diagnostic Value of Liver Biopsy."

NEW ENGLAND CENTER HOSPITAL HOUSE OFFICERS' ASSOCIATION

The New England Center Hospital House Officers' Association announces the following programs in its Evening Lecture Series:

Wednesday, October 29. The Cause of the Delay in Coagulation of Blood in Hemophilia. Dr. Leandro M. Tocantins, professor of clinical and experimental medicine, Jefferson Medical College of Philadelphia. Discussers: Drs. Mario Stefanini and William Dameshek.

Wednesday, November 19. Dyspnea. Dr. Eugene A. Stead, Jr., professor of medicine, Duke University School of Medicine. Discussers: Drs. Mark D. Altschule and Robert P. McCombs.

These programs will be held at 7 p.m. in the Stearns Auditorium of the Hospital. All interested persons are invited to attend.

NEW ENGLAND SOCIETY OF PSYCHIATRY

The fall meeting of the New England Society of Psychiatry will be held at Foxboro State Hospital, Foxboro, Massachusetts, on Wednesday, November 12.

PROGRAM

11:30 a.m.–12:30 p.m. Tour of the hospital with host to the Society, Dr. John T. Shea.
11:30 a.m.–12:30 p.m. Executive Committee meeting.
12:30–1:00 p.m. Business meeting.
1:00 p.m. Luncheon (a nominal charge will be made).
2:00 p.m. The Psychiatrist as a Witness. Dr. Winfred Overholser, superintendent, St. Elizabeth's Hospital, Washington, D. C.

E. STANLEY EMERY MEMORIAL LECTURE

The E. Stanley Emery Memorial Lecture will be presented in the amphitheater of the Peter Bent Brigham Hospital, Boston, on Wednesday, November 19, at 8 p.m. Dr. Paul B. Beeson, Ensign Professor of Medicine, Yale University School of Medicine, will speak on the subject "Fever."

POSITIONS AS MEDICAL OFFICER AT ST. ELIZABETH'S HOSPITAL

The United States Civil Service Commission has announced medical-officer examinations for the following positions in St. Elizabeth's Hospital, Washington, D. C.: rotating intern ($2,800 a year); psychiatric resident ($3,400 to $4,200 a year); and general-practice resident ($3,400 to $3,800 a year).

Appropriate education and training are required. No written test will be given. The maximum age limit is thirty-five years (waived for veterans).

Full information and application forms may be obtained from most first-class and second-class post offices, from the United States Civil Service Commission, Washington 25, D. C. Applications will be accepted until further notice by the Executive Secretary, Board of United States Civil Service Examiners, St. Elizabeth's Hospital, Washington 25, D. C.

FELLOWSHIPS AND GRANTS FOR SCHOLARS IN CANCER RESEARCH

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is accepting applications for fellowships and for grants for scholars in cancer research.

Fellowships are available to promising post-doctoral students for advanced training and experience in research in all branches of biologic, chemical and physical sciences and of investigative medicine applicable to the study of growth. Three British–American exchange fellowships are also available, through the co-operation of the British Empire Cancer Campaign Fund — the Committee will favor a proposed training program in specialized scientific areas in which superior facilities exist in Great Britain.

Applications for fellowships must be received by December 10 to be considered for the year 1953–1954. Fellowships will ordinarily begin July 1, 1953, though this date may be varied at the request of the applicant.

Applications for grants for scholars in cancer research should be submitted by an institution on behalf of a candidate prior to January 1, 1953. With these awards a grant of $6000 a year for three years is paid to the institution.

Communications should be addressed to the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 6–DECEMBER 8 AND MARCH 2–MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

OCTOBER 7–DECEMBER 9. Massachusetts Department of Mental Health. Course in Child Psychiatry (Pediatric Neuropsychiatry). Page 540, issue of October 2.

OCTOBER 26–29. National Society for Crippled Children and Adults. Page 583, issue of October 9.

OCTOBER 27–29. Medicomilitary Symposium. Page 454, issue of September 18.

OCTOBER 28–30. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 29. New England Center Hospital House Officers' Association. Page 661.

OCTOBER 29. Harvard School of Public Health. Symposium on Nutrition. Page 661.

OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

OCTOBER 30. Hampden District Medical Society. Page 623, issue of October 16.

OCTOBER 30. New England Pathological Society. Page 540, issue of October 2.

OCTOBER 30–NOVEMBER 1. Hospital for Joint Diseases. Page 583, issue of October 9.

OCTOBER 30–NOVEMBER 1. National Association for Music Therapy. Page ix, issue of July 31.

OCTOBER 31 AND NOVEMBER 1. Eastern Section of American Trudeau Society. Page 190, issue of July 31.

NOVEMBER 1–29. Springfield Hospital Educational Program. Page 623, issue of October 16.

NOVEMBER 2–7 AND 10–21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

NOVEMBER 5. Greater Boston Medical Society. Page 661.

NOVEMBER 5. Massachusetts Society of Examining Physicians. Page 661.

NOVEMBER 5–APRIL 8. Postgraduate Medical Institute. Page 452, issue of September 18.

NOVEMBER 6. New England Hospital. Page 661.

NOVEMBER 9 AND 10. American Society for the Study of Arteriosclerosis. Page 78, issue of July 10.

NOVEMBER 10–13. International Medical Assembly. Page 584, issue of October 9.

NOVEMBER 11. Springfield Academy of Medicine. Page 623, issue of October 16.

NOVEMBER 11–14. American Society of Anesthesiologists, Inc. Third Annual Refresher Course Program. The Bellevue-Stratford, Philadelphia.

NOVEMBER 12. New England Society of Psychiatry. Notice above.

NOVEMBER 14 AND 15. Diabetes Fair. Page 623, issue of October 16.

NOVEMBER 17–19. Association of Military Surgeons of the United States. Page 583, issue of October 9.

NOVEMBER 18, FEBRUARY 6 AND APRIL 3. New England Society of Anesthesiologists. Page 418, issue of September 11.

NOVEMBER 19. E. Stanley Emery Memorial Lecture. Notice above.

NOVEMBER 19. New England Center Hospital House Officers' Association. Page 661.

NOVEMBER 21. New York Tuberculosis and Health Association. Page 583, issue of October 9.

NOVEMBER 25. Norfolk District Medical Society. Page 583, issue of October 9.

DECEMBER 12 AND 13. Association for Research in Nervous and Mental Disease. Page 584, issue of October 9.

AUGUST 24–28, 1953. Eighth International Congress on Rheumatic Diseases. Page 584, issue of October 9.

DISTRICT MEDICAL SOCIETIES

HAMPDEN

OCTOBER 30. 6:30 p.m. Hotel Kimball, Springfield.

MIDDLESEX SOUTH

OCTOBER 29. 11:15 a.m. Mount Auburn Hospital, Cambridge.

NORFOLK

OCTOBER 28.
NOVEMBER 25. 8:00 p.m. John Ware Hall, Boston Medical Library.
JANUARY 27.
FEBRUARY 24.
MARCH 24.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 30

THURSDAY, OCTOBER 30

*8:30–10:00 a.m. Orthopedic Staff Conference, Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. The Pathologic Physiology of Polycythemias. Dr. William B. Castle. Stearns Auditorium, New England Center Hospital.
4:00 and 7:45 p.m. New England Pathological Society. Massachusetts Memorial Hospitals.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, OCTOBER 31

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit. 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m.–1:00 p.m. Combined Medical and Surgical Rounds. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*7:00–9:00 p.m. Combined Anesthesia Teaching Conferences of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.

(Notices concluded on page xiii)